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A LONG-TERM EVALUATION OF THE JUVENILE DIABETIC

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WITH the introduction of insulin, the lifespan of the juvenile diabetic has been greatly extended, but with the prolongation of life has come the development of vascular complications in a very high percentage of those juvenile diabetics who have had the disease long enough.[1] This report outlines our experience with a group of 150 patients diagnosed under the age of 15 years and followed in the Department of Pediatrics and later in the Metabolism Clinic of the Henry Ford Hospital for periods of between one and thirty years. Special attention will be given to forty-four, who have been followed for more than ten years after the initial diagnosis was established. The patients are for the most part from the middle economic stratum and have had the advantage of intelligent cooperation from parents.

It was felt that in looking forward to an appraisal of any program, the number of variables would be large and that diet at least should be a constant. Through the growth period, a uniform dietary plan has been followed. A first approximation of the caloric need is determined by adding 90 per cent to the basal calories predicted from the Wetzel[2] Grid. This is then varied according to the child's satisfaction and the record of his growth. The figure proves high in the younger group, but usually has to be increased for the adolescent boy, particularly the athlete, for whom basal calories multiplied by 2.2 more nearly approximate the need. In allocating the total calories for the day, provision is made for 10 per cent after school and again at bedtime. The caloric distribution of the mixture has been kept constant and derives 15 per cent from protein, 50 per cent from fat, and 35 per cent from carbohydrate. In a 2,000 calorie diet, this provides 75 Gm. of protein, 110 Gm. of fat, and 170 Gm. of carbohydrate. We are adverse to the practice of the "free diet" for two reasons: (1) in a study of self-selected diets among tuberculous adolescents in which twelve children participated, only three chose a diet sufficiently high in protein to ensure a consistently positive nitrogen balance; and (2) with a constant caloric intake, the type and amount of insulin can be better calculated so as to avoid

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serious glycosuria and insulin reactions.[3]

When classifying control, we used as criteria the number of times in coma, excluding the initial one if present, and the Benedict reaction of urines tested at home. Table I outlines these factors. Insulin reactions are difficult to measure but, for the most part, a well-controlled diabetic experiences perhaps only one of a more than mild degree every two or three years. The type of insulin used has varied through the years. At present we employ NPH insulin alone or in combination with small amounts of regular insulin given in the same syringe.

TABLE I. CLASSIFICATION OF CONTROL OF DIABETES

CONTROL	NUMBER OF TIMES IN COMA	RESULTS OF BENEDICT'S TEST ON URINE
Good	0	2 plus once a day
Fair	1	2 plus once a day
Fair to poor	2 to 3	2 to 3 plus daily
Poor	4 or more	4 plus daily

RESULTS

In the group of forty-four patients having the disease for ten or more years, twenty-six, or 59 per cent, had some of the vascular complications of the diabetic state, and eighteen, or 41 per cent, were free of any complication. The average time of the onset of the first evidence of any complication was eleven years eight months after the initial diagnosis of diabetes had been made. The average duration of follow-up on each group, those with complications and those without, was the same, fourteen years four months. When considering the group of twenty-six patients exhibiting complications, Table II shows the frequency of each of these late complications of diabetes mellitus. The degree of each of these complications varied as to severity and to physical disability produced. Three patients died of Kimmelstiel-Wilson disease,[4] and another with bilateral cataracts had such extensive retinal hemorrhages that cataract removal was not thought worth while. The relationship between control and complications is shown in Table III. Such results could have occurred by chance in less than one in one hundred times. Of interest is the fact that of the five patients with Kimmelstiel-Wilson disease, all were under poor control.

TABLE II. COMPLICATIONS AND NUMBER OF TIMES EACH WAS ENCOUNTERED AMONG TWENTY-SIX PATIENTS

COMPLICATION	NUMBER
Retinopathy	18
Albuminuria (alone)	7
Kimmelstiel-Wilson disease	5
Nephritis	3
Neuropathy	2
Hypertension	1
Cataracts	1

TABLE III. CONTROL AND COMPLICATIONS

CONTROL	NO. OF PATIENTS WITH COMPLICATIONS	NO. OF PATIENTS WITHOUT COMPLICATIONS
Good	6	11
Fair	5	5
Fair to poor	5	2
Poor	10	0
Total	26	18

The insulin and caloric requirements in the young diabetic steadily increased until after puberty, at which time both leveled off and decreased. The greatest increases occurred during the rapid growth phase that accompanies puberty. These increases are graphically illustrated in

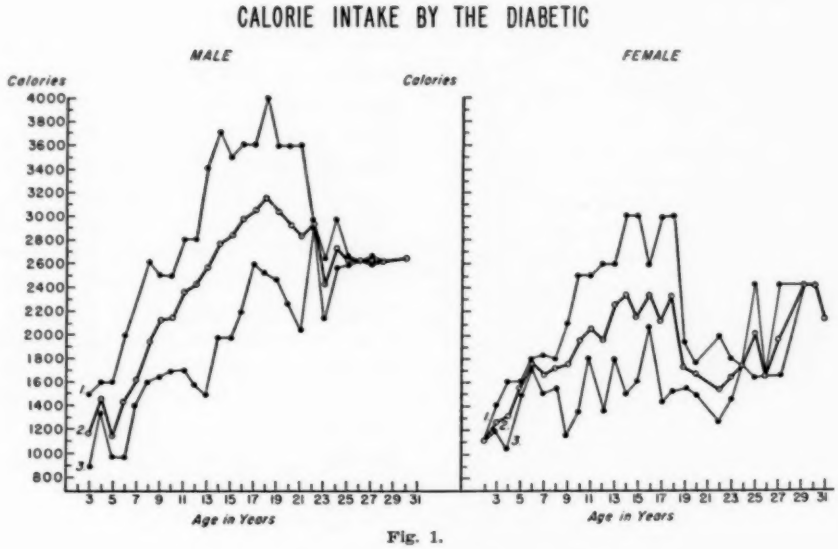
CALORIE INTAKE BY THE DIABETIC
MALE
FEMALE
Calories
Age in Years

Fig. 1.

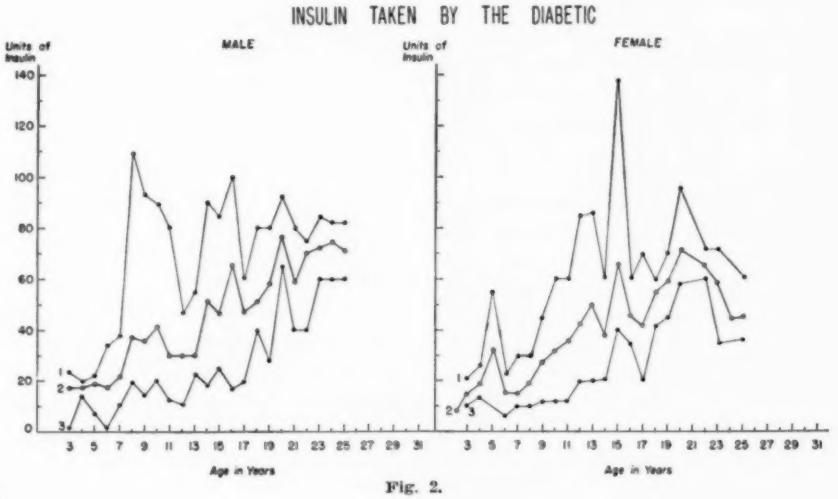
INSULIN TAKEN BY THE DIABETIC
MALE
FEMALE
Units of Insulin
Age in Years

Fig. 2.

Figs. 1 and 2, which represent information gathered from the 150 patients.

In 108 of the 150 patients an adequate evaluation of physical growth was possible. The Wetzel Grid technique[2] was employed in this survey. Normal growth was obtained in ninety-five patients, 78 of whom were classified as under fair or good control. The remaining seventeen, despite poor or fair to poor control, grew normally. There were thirteen who fell outside the norms for proper growth, four under fair or good control and nine under poor or fair to poor control. Table IV summarizes this information. There were ten deaths in our total series of 150 patients, six in coma, three of Kimmelstiel-Wilson disease, and one of tuberculosis.

TABLE IV. GROWTH AND ITS RELATIONSHIP TO CONTROL

		CONTROL	
GROWTH	NUMBER	FAIR OR GOOD	POOR OR FAIR TO POOR
Normal	95	78	17
Abnormal	13	4	9

DISCUSSION

The trend in the long-term outcome for the childhood diabetic is the same as that indicated in our previous communication[5] and is in agreement with the data published by Walker,[6] by Post and Stickle,[7] and by Root and coworkers[8]: that is, the better the control the fewer are the complications, with the most common of these being retinal vessel changes and punctate retinal hemorrhage.[9] Patients with good control are far more likely to maintain normal growth patterns.

The controversy between "free" and "controlled" regimes in the management of the diabetic is, we believe, swinging in favor of the controlled type, because of the increasing number of reports in addition to those already cited that show the direct relationship between good control and a minimum of complications.[10-12] To obtain this control, a diet allowing a moderate amount of carbohydrate can be used with sucess. Lichtenstein[13] when writing on the "free diet" in childhood diabetes gives his results on the basis of ten years' experience. He states that the number of complications encountered were few. We must, however, remember that seldom do any of the vascular changes make themselves evident, control not being considered, until the child has had the disease at least ten years.

The cause of the complications is a matter certainly far from settlement. Styron[14] proposes that their occurrence depends on (1) duration of the disease, (2) the degree of control, and (3) an X factor, this last being the subject of much investigation. Perhaps the X factor is an integral part of a generalized degenerative vascular disease process of which diabetes mellitus is but a part, as suggested by Peters.[15] John[16] points out that when a person runs a positive Benedict's reaction in the urine once a day we can assume that he is hyperglycemic about six hours out of twenty-four. He goes on to say that a normal person with his postprandial hyperglycemia has a relatively high blood sugar for the same number of hours. In the everyday management of these children it is our opinion, therefore, that a program providing a moderate amount of carbohydrate and allowing a two plus

Benedict's reaction once a day to guard against insulin reactions affords a good middle ground to follow between a truly free program and an extremely rigid one.

The caloric and insulin requirements are not stable in these young and growing patients. Each shows a steady increase until after puberty. Our findings along these lines are in accord with those of Kelly and associates.[17] Such changes make close observation by the attending physician mandatory.

On the program as outlined, our patients have enjoyed a good degree of success both in physical growth and in the psychological acceptance of their disease. The small effort expended by the physician in helping his young diabetic to keep under proper control will be repaid many times over.

SUMMARY

In the regulation of diabetes mellitus in children, control is of the utmost importance when prevention of serious vascular complications is considered.

Retinopathy and albuminuria were the most frequently encountered vascular complications.

Complications of this sort first became detectable at an average of eleven years eight months after the initial diagnosis.

There is an increased need for insulin and calories as growth progresses. A peak is reached at puberty, followed by a drop and then stabilization of both insulin and caloric requirements.

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INTRATHECAL HYDROCORTISONE IN THE TREATMENT OF TUBERCULOUS MENINGITIS

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THE introduction of isoniazid administered in combination with streptomycin in the treatment of tuberculous meningitis (T.B.M.) has considerably improved and simplified the therapeutic scheme and prognosis of the disease.

Clinical and experimental evidence supports the thesis that the action of isoniazid increases in a dynamic way when administered in conjunction with streptomycin. Furthermore its antiallergic properties are well established,[1] and the beneficial effects of the drug are noted on the clinical course of the disease, as well as on the laboratory and histologic features.

The treatment of tuberculous meningitis has not attained as yet a conclusive and ideal solution. A considerable number of patients in the infant age group, with advanced and severe forms of the disease, present multiple therapeutic difficulties.

The introduction of cortisone in the treatment of tuberculous meningitis undoubtedly marks progress in the fight against the disease, as the clinical trials of corticosteroids combined with suitable chemotherapy are encouraging.[2]

Recently the use of cortisone, administered systemically or locally, has been suggested, and it is postulated that its use simultaneously with the antibiotics minimizes the dangers of blocks and obstructions in the circulation of the cerebrospinal fluid.

This report deals with our experience in the use of intrathecal cortisone in the treatment of T.B.M., compared with standard methods of treatment.

MATERIAL AND METHODS

Eighty-two children with tuberculous meningitis were treated at St. Sophie's Children's Hospital of the University of Athens during a two-year period.

Of these, twenty-four received the standard therapy of intramuscular and intrathecal streptomycin and isoniazid. Twenty-nine were given cortisone intramuscularly in addition.

In twenty-nine, intrathecal streptomycin was discontinued and replaced by I.M. and/or I.T. cortisone, in addition to I.T. and I.M. isoniazid, and I.M. streptomycin. The groups, although not formally controlled, are comparable to each other.

By our method streptomycin was administered intramuscularly at a dose of 30 to 40 mg. per kilogram of body weight, and isoniazid intramuscularly at 10 to 20 mg. per kilogram of body weight and intrathecally 6 mg. daily for a period of one to three months. The dose of I.M. cortisone was 25 to 75 mg. daily for twenty to

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twenty-five days, and that of I.T. cortisone was 5 mg. once a day for about three weeks.*

RESULTS

Standard Treatment.—All patients admitted in 1954 received the standard treatment of streptomycin-isoniazid intrathecally and intramuscularly (Table I).

The cerebrospinal fluid protein returned to normal at an average period of 87.7 days, while sugar values became normal after an average 18 days' period.

The patient in Case 11 developed a spinal block and hydrocephalus.

A boy admitted as a relapsed tuberculous meningitis patient (Case 8) was cured by intensive streptomycin-isoniazid therapy.

The child in Case 9 was admitted in semicomatose condition, with signs of spastic hemiplegia. He showed an uneventful recovery.

In Case 18 a left hemiplegia and papilledema developed, which disappeared under treatment.

The infant in Case 22, in addition to tuberculous meningitis, had miliary tuberculosis. He died eight days after admission.

TABLE I. STANDARD THERAPY IN TUBERCULOUS MENINGITIS (STREPTOMYCIN-INH, INTRAMUSCULARLY AND INTRATHECALLY)

CASE	AGE	CLASSIFICATION ACCORDING TO SEVERITY	PROTEIN RETURNED TO NORMAL (DAYS) C.S.F.	DAYS IN HOSPITAL	RESULTS OF TREATMENT
1	7 yr.	Intermediate	120	180	Cured
2	8 yr.	Severe	50	100	Cured
3	2½ yr.	Intermediate	160	180	Cured
4	10 yr.	Intermediate	100	135	Cured
5	14 yr.	Early	40	50	Cured
6	18 mo.	Early	65	75	Cured
7	6 yr.	Early	30	50	Cured
8	12 yr.	Early	50	75	Cured
9	12 yr.	Severe	150	170	Cured
10	5 yr.	Intermediate	70	75	Cured
11	16 mo.	Severe	120	130	Hydrocephalus
12	2 yr.	Severe	80	90	Cured
13	7 yr.	Severe	70	75	Cured
14	5 yr.	Early	45	60	Cured
15	3 yr.	Intermediate	90	100	Cured
16	2 yr.	Severe	110	140	Cured
17	10 yr.	Intermediate	110	130	Cured
18	5 yr.	Severe	105	140	Cured
19	6 yr.	Intermediate	70	95	Cured
20	18 mo.	Intermediate	85	120	Cured
21	13 mo.	Severe	–	3	Death
22	7 mo.	Severe	–	8	Death
23	17 mo.	Severe	–	14	Death
24	26 mo.	Severe	–	84	Death

This group consisted of twenty-four cases. Eleven were classified by clinical and laboratory criteria as severe, eight as intermediate, and five as early.

There were four deaths in this group (16.6 per cent). Two of the deaths occurred within the first week of admission. Three of the deaths occurred in infants, and one in a girl of 26 months.

*We wish to thank Dr. O'Donovan of the Upjohn Company for the generous donation of Upjohn's Cortef used in this study.

All remaining patients recovered uneventfully.

Detailed study of electroencephalograms revealed diffuse meningoencephalitic abnormalities which disappeared after the clinical and laboratory findings became normal.

On the average, 90 days were required for normalization of electroencephalograms.

Clinical improvement of the patients under cortisone was striking, while the laboratory data revealed protein values returning to normal at an average period of 71.5 days, and sugar values after a 13-day period.

There were five deaths in the group (17.2 per cent). Three of the deaths occurred within the first week of admission. All patients who died were in the infant age group, with the exception of one 5½-year-old boy. One patient who received cortisone without antibiotic cover died of multiple pulmonary staphylococcal abscesses and empyema.

No spinal blocks were noted.

TABLE II. STANDARD THERAPY (STREPTOMYCIN-INH) PLUS CORTISONE INTRAMUSCULARLY IN TUBERCULOUS MENINGITIS

CASE	AGE	CLASSIFICATION ACCORDING TO SEVERITY	PROTEIN RETURNED TO NORMAL (DAYS)	DAYS IN HOSPITAL	RESULTS OF TREATMENT
1	14 yr.	Intermediate	110	130	Cured
2	21 mo.	Early	40	55	Cured
3	5 yr.	Early	25	45	Cured
4	4 yr.	Intermediate	85	110	Cured
5	3 yr.	Severe	40	60	Cured
6	13 yr.	Severe	125	140	Cured
7	19 mo.	Intermediate	105	115	Cured
8	10 mo.	Intermediate	90	105	Cured
9	8 yr.	Early	40	45	Cured
10	13 yr.	Severe	100	120	Cured
11	5 yr.	Severe	70	90	Cured
12	6 mo.	Severe	50	105	Cured
13	18 mo.	Severe	120	150	Cured
14	3 yr.	Severe	60	100	Exopyramidal syndrome
15	10 yr.	Severe	80	80	Cured
16	11 yr.	Intermediate	40	60	Cured
17	3 yr.	Intermediate	60	80	Cured
18	7 yr.	Severe	75	90	Cured
19	16 mo.	Severe	70	90	Cured
20	11 yr.	Early	45	60	Cured
21	19 mo.	Severe	80	130	Cured
22	10 mo.	Intermediate	120	145	Cured
23	12 mo.	Intermediate	100	110	Cured
24	7 mo.	Early	15	40	Cured
25	4 mo.	Severe	–	58	Death
26	12 mo.	Severe	–	36	Death
27	6 mo.	Severe	–	4	Death
28	28 mo.	Severe	–	13	Death
29	5½ yr.	Severe	–	8	Death

Standard Treatment Plus Cortisone.—The next twenty-nine patients received cortisone I.M. in the dosage given above, in addition to the usual antibiotic therapy (Table II).

Four of the patients of this group were classified as early, seven as intermediate, and fourteen as severe cases.

Eighteen of the patients receiving cortisone intramuscularly showed a mild febrile reaction and a slight increase of C.S.F. findings upon discontinuation of steroid therapy. There were a moderate increase of cellular elements and a slight increase of protein, while the sugar values remained unaltered. These findings disappeared when cortisone therapy was resumed for four to five additional days. In five cases a short course of intramuscular cortisone was required more than twice.

Case 13 involved optic atrophy and blindness. The patient was discharged with vision restored to normal.

Case 14 also showed optic atrophy. This patient remained spastic and decerebrated upon completion of therapy.

The patient in Case 15, while under intensive treatment, developed *Hemophilus influenzae* meningitis. She had a stormy but uneventful recovery.

In Case 17, the development of hepatitis and Schönlein-Henoch's purpura was noted while the patient was under treatment. Recovery was uneventful.

The patient considered in Case 28 died thirteen days after admission. Autopsy revealed hydrocephalus and generalized tuberculosis, multiple tubercles being found in the brain.

Electroencephalographic tracings were restored to normal before the laboratory findings became normal, and considerably earlier than in the group of patients treated without cortisone. An average of 75 days was required for the restoration of electroencephalograms to normal.

Intrathecal Cortisone.—In the next twenty-nine patients streptomycin was discontinued intrathecally and replaced by cortisone (Table III).

Patients were alternated, those with even numbers receiving I.T. isoniazid plus standard therapy intramuscularly, as well as sterile alcoholic solutions of hydrocortisone intrathecally, and those with odd numbers received in addition cortisone intramuscularly. There were no significant differences in the results between patients of the two groups.

Seven of the patients were classified as early, twelve as intermediate, and ten as severe.

Intrathecal hydrocortisone was given at a dosage of 5 mg. once a day for three weeks. Generalized reactions were not encountered. A cellular reaction of the C.S.F. to the intrathecal infusion of the drug was not observed.

In this group of patients there were four deaths, two occurring one week after admission of the patients to the hospital (mortality, 13.7 per cent).

No obstructions to the circulation of the C.S.F. were noted.

In two patients (Cases 12 and 13) obstruction which appeared initially was relieved by cisternal infusion of cortisone.

Protein and sugar values of the C.S.F. were rapidly restored to normal. Thus the protein returned to normal in an average 51.3 days' period in patients receiving cortisone intrathecally and in 57.8 days in cases in which the drug was administered both I.T. and I.M. An average of 7 days was required for the abnormally low sugar to return to normal.

Electroencephalographic abnormalities disappeared rapidly under this form of therapy. An average of 55

days was required for the restoration of electroencephalograms to normal.

The average hospitalization of patients belonging to this group was 71.2 days, as compared to 79.2 for patients receiving steroid therapy both I.T. and I.M., and 102 days in cases treated by the standard way of treatment plus I.M. cortisone.

hydrocortisone produced an astonishingly rapid recovery. He was discharged, entirely normal, after a little more than a two-month period.

In Case 14 chicken pox developed while the child was under treatment. At that time a mild epidemic of chicken pox occurred among our tuberculous meningitis patients.

TABLE III. THE USE OF INTRATHECAL HYDROCORTISONE IN ADDITION TO STREPTOMYCIN-INH BUT WITHOUT INTRATHECAL STREPTOMYCIN

CASE	AGE	CLASSIFICATION ACCORDING TO SEVERITY	ROUTE	PROTEIN RETURNED TO NORMAL (DAYS)	DAYS IN HOSPITAL	RESULTS OF TREATMENT
1	7 yr.	Early	I.T.	25	50	Cured
2	8 yr.	Intermediate	I.T.	50	65	Cured
3	8 yr.	Early	I.T.	25	45	Cured
4	10 mo.	Severe	I.T.	50	70	Cured
5	6 yr.	Intermediate	I.T.	45	60	Cured
6	2 yr.	Intermediate	I.T.	45	65	Cured
7	10 yr.	Intermediate	I.T.	45	65	Cured
8	4 yr.	Early	I.T.	40	65	Cured
9	7 yr.	Intermediate	I.T.	69	69	Cured
10	9 yr.	Early	I.T.	50	65	Cured
11	6 yr.	Early	I.T.	25	60	Cured
12	18 mo.	Severe	I.T.	135	170	Cured
13	11 mo.	Intermediate	I.T.		Still in hospital	
14	2½ yr.	Early	I.T.-I.M.	55	75	Cured
15	3 yr.	Severe	I.T.-I.M.	70	90	Cured
16	3 yr.	Severe	I.T.-I.M.	50	75	Cured
17	12 yr.	Intermediate	I.T.-I.M.		Still in hospital	
18	27 mo.	Severe	I.T.-I.M.	30	55	Cured
19	8 yr.	Intermediate	I.T.-I.M.	90	110	Cured
20	10 yr.	Intermediate	I.T.-I.M.		Still in hospital	
21	28 mo.	Intermediate	I.T.-I.M.	55	70	Cured
22	13 mo.	Intermediate	I.T.-I.M.	55	70	Cured
23	11 mo.	Severe	I.T.-I.M.		Still in hospital	
24	11 mo.	Early	I.T.	18	30	Cured
25	7 mo.	Intermediate	I.T.		Still in hospital	
26	12 yr.	Severe	I.T.	–	8	Death
27	5 yr.	Severe	I.T.-I.M.	–	95	Death
28	23 mo.	Severe	I.T.-I.M.	–	8	Death
29	6 yr.	Severe	I.T.-I.M.	–	90	Death

In Case 2, upon discontinuation of intrathecal infusions of hydrocortisone a moderate clinical and laboratory aggravation of the patient's condition was noted. Cortisone was resumed intrathecally and a gradual restoration to normal occurred.

Case 4 was that of a 10-month-old infant with an unusually severe picture of tuberculous meningitis. Hemiplegia was present. Intrathecally,

It was noted that the concurrent infectious disease ran a more severe and more prolonged course, while the course of tuberculous meninigtis remained unchanged. All patients with chicken pox and tuberculous meningitis continued receiving intrathecal cortisone and recovered uneventfully.

The boy in Case 15 was in a comatose condition when admitted. He presented, in addition to his severe

form of T.B.M., an extensive miliary tuberculosis. He recovered uneventfully within a three-month period.

Case 9 also showed miliary tuberculosis in addition to tuberculous meningitis. Recovery was uneventful.

The degree of hypersensitivity to old tuberculin was evaluated under I.T. and/or I.M. cortisone treatment.

Our results though not conclusive point to a rapid diminution of hypersensitivity under cortisone therapy, which interestingly enough coincides with an amelioration of the clinical and laboratory findings of the disease. It remains to be seen whether the transient elevation of C.S.F. findings, which occasionally is noted during therapy, is accompanied by an accentuation of the tuberculin reaction.

The titer of the Middlebrook-Dubos reaction revealed no significant changes during I.M. or I.T. cortisone treatment, when compared with patients handled by standard ways of therapy.

DISCUSSION

The question of the use of cortisone during the course of infectious diseases is of great interest and importance.

In spite of the fact that the early results of the use of cortisone in experimental tuberculosis were unfavorable, clinical trials of corticosteroids combined with suitable chemotherapy were encouraging. The major effect of these drugs in infections appears to be a suppression of the usual inflammatory response of the body with impairment of granulation tissue formation, macrophage activity, and fibroplastic repair.

Because of a lymphocytolysis which is observed during long-term cortisone therapy, antibody formation may be depressed, according to some workers, but it is believed today by most investigators that the adrenal steroids do not act directly on the antigen-antibody mechanisms except in a nonspecific manner by limiting the inflammatory response.

A few writers have recommended that corticotropin or cortisone be used in the specific treatment of infections in conjunction with appropriate antimicrobial therapy, especially in overwhelming toxic states in which immediate improvement of the patient's symptoms is imperative, e.g., pneumococcal pneumonia,[3] typhoid fever,[4] tuberculous meningitis,[5] eye inflammations,[6] etc.

Recently Wasz-Höckert[7] has been extensively using hydrocortisone intrathecally in patients with T.B.M. The results have been described as encouraging.

In our group of patients cortisone administered intrathecally in combination with INH and streptomycin intramuscularly and INH intrathecally produced a significant improvement of (a) the patient's general condition and (b) the changes in the C.S.F.

All patients given cortisone intramuscularly or intrathecally showed a striking clinical improvement. Their appetites improved, and the initial aggravation of tuberculous meningitis encountered in patients receiving intensive intrathecal antituberculous therapy was avoided.

Though an alcoholic solution was used (Cortef), local or generalized reactions to intrathecal or cisternal infusions were not encountered.

Neurological complications were few in all three groups and therefore further experience is required to establish hydrocortisone's value as an agent preventing mechanical obstructions to the circulation of the C.S.F. caused by exudate or fibrous tissue.

The duration of treatment with hydrocortisone intrathecally was three weeks. Occasionally, because of an aggravation of C.S.F. findings on discontinuation of steroid therapy, short courses of intrathecal infusions with cortisone were resumed. This proved beneficial in most of the cases, and the protein, as well as cellular elements, returned to normal.

One patient receiving moderate doses of I.M. cortisone without the protection of antimicrobial antibiotics died of septicemia. Autopsy revealed multiple staphylococcal pulmonary abscesses.

The danger of lighting up an old infection or acquiring a new one is real, and appropriate antibiotics must be given while the patient is receiving intramuscular or intrathecal cortisone, and for three to four days after withdrawal of the hormone.

We believe that intrathecally administered hydrocortisone in the treatment of tuberculous meningitis has important advantages and merits further use.

SUMMARY

In this report a group of patients with tuberculous meningitis treated by standard methods of therapy is compared with a group of patients with the same disease who received in addition cortisone intramuscularly, and with a third group in which hydrocortisone was administered intramuscularly and/or intrathecally.

We believe that I.M. cortisone has a beneficial effect on the clinical course and laboratory findings.

Though we do not have enough evidence to support the claim that I.T. hydrocortisone prevents the occurrence of neurological complications, we nevertheless think that this mode of therapy is superior to all others, and that astonishing results occur in apparently hopeless situations.

In two of our cases an early block in the circulation of the C.S.F. was relieved by cisternal infusions of hydrocortisone.

The rapid clinical and laboratory improvement in some cases of patients with T.B.M. receiving I.T. hydrocortisone warrants a more extensive trial of its use.

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NOCARDIOSIS IN CHILDHOOD

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ST. LOUIS, MO.

THE ability of the aerobic actinomycetes to produce both localized and systemic disease in man is well recognized. A review of the present world's literature reveals eleven reported cases of nocardiosis in the pediatric age group.[1-11] It is the relative infrequency of the infection and the fact that it continues to be overlooked in chronic bronchopulmonary disease which prompted this report.

CASE REPORT

J. F., a Negro male, was admitted to the St. Louis County Hospital in January, 1953, at 9 months of age, with a history of cough, fever, diarrhea, and progressive enlargement of the abdomen, of two months' duration. Past history revealed that he had been treated for a pustular eruption of the buttocks in June, 1952. He had been hospitalized in September, 1952, because of a respiratory infection, diarrhea, and malnutrition which responded well to conventional therapy. Family history revealed that a sibling had died in early 1952, with an illness characterized by multiple subcutaneous abscesses and the clinical picture of sepsis; a second sibling had a history of discoid lupus erythematosus. Physical examination showed an undernourished infant with generalized lymphadenopathy, hepatosplenomegaly, and signs of bilateral pulmonary consolidation. Laboratory studies revealed a polymorphonuclear leukocytosis, a mild hypochromic anemia, repeatedly normal urine analyses, a negative blood Kahn test, normal blood chemistries and serum electrolytes, and normal liver function tests. Tryptic activity was normal in the stools and in duodenal juice. Bone marrow examination showed only erythroid hyperplasia. Chest x-ray (Fig. 1) at the time of admittance revealed bilateral hilar enlargement and pulmonary infiltration, with deviation of the trachea to the right. Repeated O.T., P.P.D., and histoplasmin skin tests were negative. Repeated blood cultures were sterile and sputum cultures yielded only normal flora. His course was febrile, unresponsive to penicillin and streptomycin, but responsive to sulfonamides (Fig. 2). He showed persistent hepatosplenomegaly and bilateral pulmonary infiltration at the time of discharge.

The patient was followed in the outpatient department and during repeated hospital admittances at the St. Louis County Hospital during the subsequent three years. His course was that of an obscure chronic pulmonary disease characterized by persistent cough and intermittent septic-type fever, hepatosplenomegaly, generalized lymphadenopathy, clinical and roentgenological evidence of remissions and exacerbations, and the gradual development of pulmonary insufficiency (Figs. 2 and 3). The chronicity of the disease was constantly reflected in his persistent polymorphonuclear leukocytosis, anemia, and growth failure (Figs. 2 and 3). The persistence and gradual progression of the chronic pulmonary disease are evident from the representative chest x-rays shown in Figs. 4 to 9.

From the Department of Pediatrics, Washington University School of Medicine, the St. Louis Children's Hospital, and St. Louis County Hospital.

During the course of his illness he was repeatedly evaluated for fibrocystic disease but he showed stool and duodenal tryptic activity and normal sweat electrolytes. Bronchograms and repeated bronchoscopic examinations revealed no abnormality. Thorough hematological evaluation on numerous occasions revealed no evidence of hemolysis, bone marrow depression, or an abnormal hemoglobin. A gamma globulin deficiency was considered but excluded on the basis of a normal gamma globulin on two occasions. Liver function studies were carried out at intervals and revealed positive cephalin flocculation and thymol turbidity tests. During the last year of illness liver function tests were within normal limits except for a progressive hypoprothrombinemia and evidence of abnormal Bromsulphalein retention. Amyloidosis secondary to chronic pulmonary suppuration was considered late in the course of the patient's illness, and Congo red test showed 44 per cent dye retention. A gum biopsy was negative. An inguinal lymph node biopsy in early 1954 showed only reactive hyperplasia. A subsequent popliteal node biopsy revealed focal suppurative necrosis and chronic granulation reaction; cultures yielded no growth.

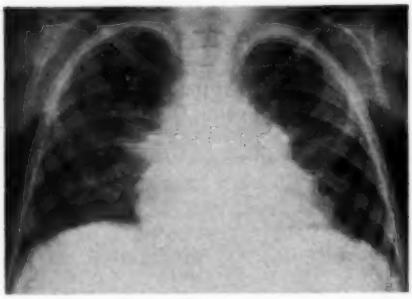

Fig. 1.—Chest x-ray, January, 1953, showing bilateral pulmonary infiltration and hilar lymphadenopathy.

Repeated blood and bone marrow cultures were sterile throughout the course of the patient's illness. Routine febrile agglutinations were constantly negative. In September, 1953, a culture of bronchial secretions grew alpha streptococci and a scant growth of coagulase-negative staphylococci. Repeated nose and throat cultures showed only normal flora. *Proteus mirabilis* and *Staphylococcus albus* were cultured from a superficial pustule of the skin in May, 1954. Intermittent pyuria was evident during 1954 and 1955, but repeated urine cultures were sterile. Sputum, bronchial secretions, bone marrow, blood, and gastric juice were examined and cultured repeatedly for fungi and acid-fast bacilli, with negative results.

In May, 1954, chest x-ray revealed evidence of cavitation or abscess formation in the lower portion of the right upper lobe (Fig. 6). In spite of negative tuberculin skin tests and lack of a bacteriological diagnosis, he was started on antituberculous drugs at that time. In September, 1954, acid-fast bacilli resembling tubercle bacilli were cultured from gastric washings but guinea pig inoculation was negative. In October, 1954, an equivocally positive O.T. patch test was reported, but repeated patch tests and intradermal skin tests at that time were negative. In December, 1954, acid-fast bacilli were seen on a smear of unconcentrated gastric juice, but the culture and guinea pig inoculations were negative. In August, 1955, after fifteen months of antituberculous therapy, a second positive O.T. patch test was noted, but repeated patch and intradermal skin tests were again negative. The patient's clinical and roentgenological courses were atypical of treated tuberculosis, as shown by the persistent pulmonary infiltration, persistence of his febrile course, and continued remissions and exacerbations (Figs. 2 and 3, 7 to 9). Antituberculous therapy was discontinued in September, 1955, after sixteen months.

In November, 1955, the patient entered the hospital, his terminal admittance, because of persistent cough,

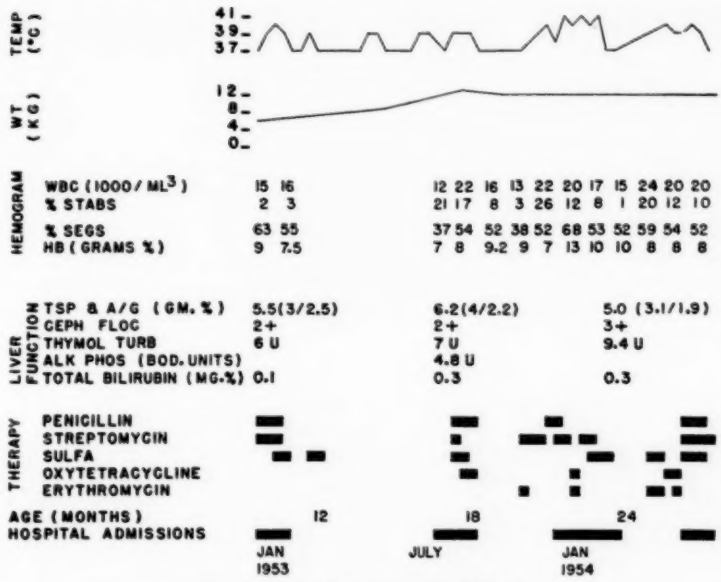
TEMP (°C)
41
39
37
WT (KG)
12
8
4
0
HEMOGRAM
WBC (1000/ML3) 15 16 12 22 16 13 22 20 17 15 24 20 20
% STABS 2 3 21 17 8 3 26 12 8 1 20 12 10
% SEGS 63 55 37 54 52 38 52 68 53 52 59 54 52
HB (GRAMS %) 9 7.5 7 8 9.2 9 7 13 10 10 8 8 8
LIVER FUNCTION
TSP & A/G (GM. %) 5.5(3/2.5) 6.2(4/2.2) 5.0 (3.1/1.9)
CEPH FLOC 2+ 2+ 3+
THYMOL TURB 6 U 7 U 9.4 U
ALK PHOS (BOD. UNITS) 4.8 U
TOTAL BILIRUBIN (MG.%) 0.1 0.3 0.3
THERAPY
PENICILLIN
STREPTOMYCIN
SULFA
OXYTETRACYCLINE
ERYTHROMYCIN
AGE (MONTHS) 12 18 24
HOSPITAL ADMISSIONS
JAN 1953
JULY
JAN 1954

Fig. 2.—Hospital course of patient.

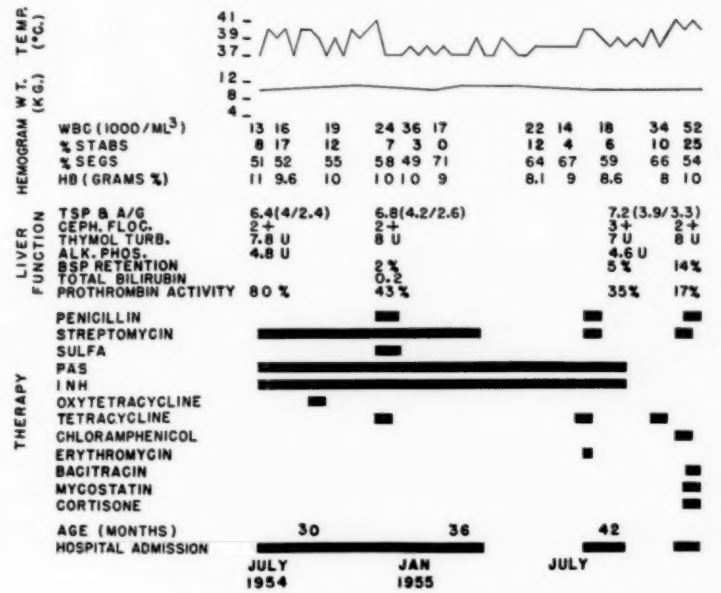

Fig. 3.—Hospital course of patient.

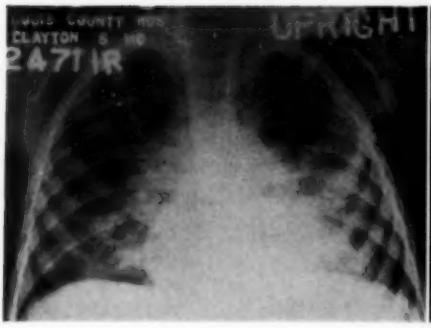

Fig. 4. Fig. 5.

Fig. 4.—Chest x-ray, August, 1953, showing progressive bilateral infiltration.
Fig. 5.—Chest x-ray, January, 1954, showing further progression of pulmonary disease.

Fig. 6. Fig. 7.

Fig. 6.—Chest x-ray, May, 1954, showing abscess formation (arrow) in the lower portion of right upper lobe.
Fig. 7.—Chest x-ray, October, 1954, revealed persistent area of radiolucency in right upper lobe with interval clearing of the infiltration in the right lung field.

Fig. 8. Fig. 9.

Fig. 8.—Chest x-ray, January, 1955, revealed partial clearing of infiltration in the left lung field.
Fig. 9.—Chest x-ray, December, 1955, revealed opacification of the left lung with loculated empyema.

fever, and increasing dyspnea. Examination at that time revealed a dyspneic, tachypneic, cyanotic, and malnourished child showing signs of bilateral pulmonary consolidation, pulmonary osteoarthropathy, generalized lymphadenopathy, and hepatosplenomegaly. Chest x-ray revealed diffuse infiltration throughout the right lung and in the posterior aspect of the left lower lobe. He was treated with multiple antibiotics with no effect upon his septic course and progressive pulmonary insufficiency. A chest x-ray on the seventeenth hospital day showed opacification of the left lung, with loculated empyema fluid (Fig. 9). Repeated thoracenteses revealed no pleural fluid or exudate. He was tried on cortisone with no clinical effect. The patient died in respiratory failure on Dec. 25, 1955. Among the clinical impressions at the time of his death were those of a staphylococcal pneumonia and sepsis, a disseminated mycosis, chronic Freidländer's pneumonia, and histiocytosis.

Necropsy Findings.—

Gross examination: Post-mortem examination was performed six hours after death. The left pleural cavity was filled with loculated areas of thick, tenacious, yellow pus which could not be drawn into a naked syringe; the remaining pleura was adherent to the lung. The suppurative process extended into the mediastinum anterior to the esophagus, with involvement of the pericardial surface. The right pleural cavity contained no fluid but the pleural surface showed many adhesions. The thyroid gland showed many small abscesses which exuded thick yellow pus, the left lobe being completely replaced by the suppurative process. The lungs (Fig. 10) weighed 700 grams. The left lung was almost completely replaced by yellow, friable, suppurative tissue; only the lower one-third of the left lower lobe showed tissue resembling normal lung tissue. The right lung had many adhesions and showed a nodular, yellowish consolidation

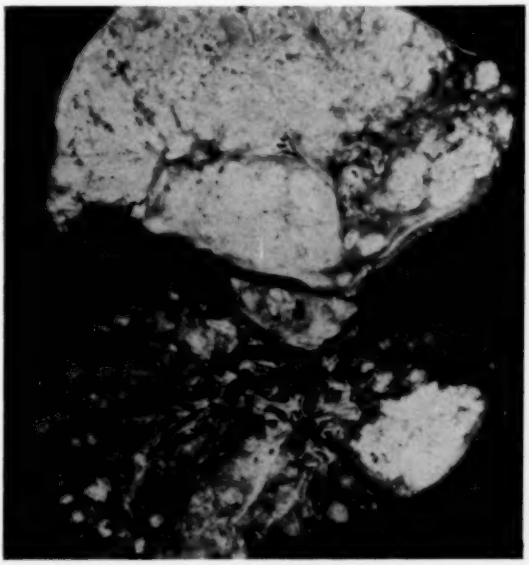

Fig. 10.—Lungs showing extensive bilateral involvement.

throughout. The tracheobronchial tree contained a small amount of thick yellow pus and could not be traced on the left side. The spleen (Fig. 11) weighed 80 grams and showed multiple lobe and the left lobe revealed multiple discrete abscesses exuding a yellowish pus. The left and right kidneys weighed 50 and 55 grams, respectively, each showing multiple cortical ab-

Fig. 11.

Fig. 12.

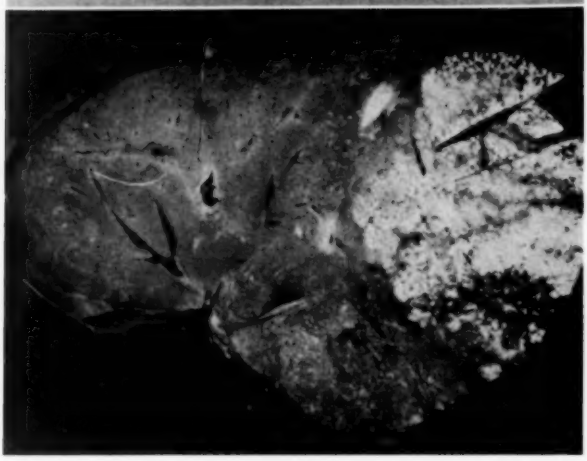

Fig. 11.—Spleen showing nodular infiltration throughout.
Fig. 12.—Liver showing extensive replacement of the left lobe with nodular infiltrate.

2 to 4 mm. yellow abscesses. The liver (Fig. 12) weighed 770 grams and the right lobe was almost completely involved by soft, yellow, confluent abscesses. The remainder of the right scesses. The remaining organs were unremarkable.

Microscopic examination: Lung tissue for section was, unfortunately, inadvertently discarded. The thyroid

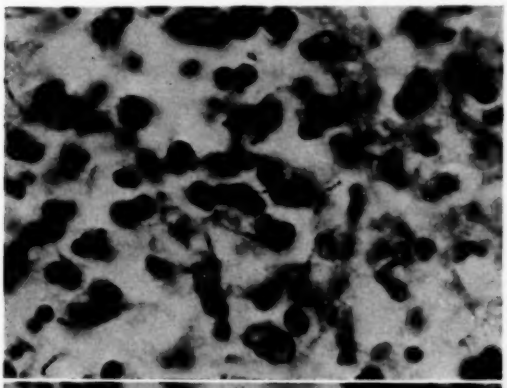

Fig. 13.

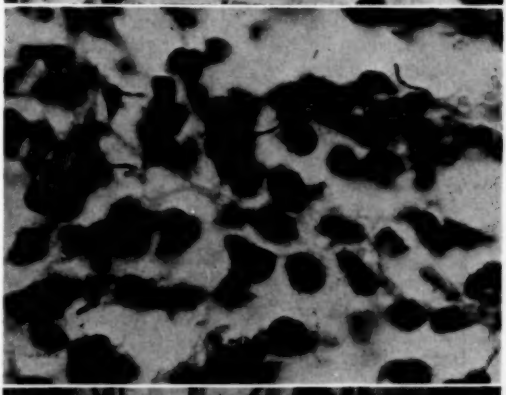

Fig. 14.

Fig. 15.

Fig. 13.—Microscopic section of liver showing gram-positive filamentous and branching *N. asteroides.*

Fig. 14.—Microscopic section of spleen showing gram-positive filamentous and branching *N. asteroides.*

Fig. 15.—Microscopic picture revealing mycelial growth of the isolated *N. asteroides.*

gland showed multiple discrete and confluent abscesses composed of densely packed neutrophils with scattered lymphocytes and macrophages. All lesions showed a marked degree of central and peripheral necrosis. Acid-fast and Gram-stained sections of thyroid revealed no organisms. Confluent and focal abscesses of the liver showed much necrosis, with solid neutrophilic infiltration, and only small islands of normal liver tissue; many gram-positive, nonacid-fast, elongated, filamentous, branching organisms were seen throughout the involved portions of the liver (Fig. 13). There was little or no evidence of scarring, fibrosis, granuloma formation, giant cells, or epithelioid cells. The spleen showed multiple abscesses similar to those seen in the liver. Organisms identical to those seen in the liver were scattered throughout the spleen (Fig. 14). Lymphoid follicles showed focal amyloid deposition. The kidneys showed focal cortical abscesses similar to those seen elsewhere.

Smears of the pus from the left lung revealed gram-positive, nonacid-fast, branching, filamentous organisms. Exudate from the lungs, liver, spleen, and thyroid at the time of autopsy yielded a pure growth of *Nocardia asteroides* within twenty-four hours. The organisms grew under aerobic conditions on Sabouraud's broth, Littman's agar, blood agar, proteose-peptone broth, thioglycollate, chocolate agar, EMB plates, a pour plate, and on Petragnani's medium. Fig. 15 represents a smear taken from Sabouraud's media, revealing the typical filamentous, branching organisms. The organism was identified both by the Department of Mycology of the Washington University School of Medicine and by the Missouri State Laboratories. Mice were inoculated intraperitoneally with the organism. The animals were sacrificed after sixteen days, at which time *N. asteroides* was isolated from both liver and spleen. The organism showed no definite acid-fast property on repeated transfer or animal passage.

REVIEW OF THE LITERATURE

The aerobic actinomycetes were first described in 1888 by Nocard[12] who isolated the organism in "farcin du boeuf," a disease seen in cattle, previously suspected as being of tuberculous etiology. Eppinger[13] described the first human infection in 1890. The organism was then known as *Cladothrix asteroides.* It has since been known as *Streptothrix eppingerii, Streptothrix nocardii, Streptothrix asteroides, Oospora asteroides, Actinomyces asteroides, Nocardia farcini,* and *Nocardia asteroides.* During the late nineteenth and early twentieth centuries, Vincent,[14] Wright,[15] Musgrave and associates,[16] and Foulerton[17-19] added much to our knowledge of this fungus, and their descriptions were the first to emphasize the inconstancy of the acid-fast property. Feistmantel,[20] after careful study of the cultural variation, tissue pathology, and acid-fast property of the organism, first asserted its close relationship to the tubercle bacillus on the one hand and to the anaerobic actinomycetes on the other.

Henrici and Gardner[21] collected twenty-six cases from the literature in 1921; thirty-two reported cases were cited in a review by Kirby and McNaught[22] in 1946. The most recent review is that of Wichelhausen and co-workers[23] who reviewed the clinical features of sixty-two reported cases in 1954.

A careful search of the world's literature at present reveals ninety-five established cases of nocardiosis (Table I.). Infections confined to the skin and subcutaneous tissues, including Madura foot, are excluded from this review. Most of the recorded cases

TABLE I. REPORTED CASES OF NOCARDIOSIS

REPORT	YEAR	SEX	AGE (YR.)	ORGANS INVOLVED	CULTURE	DURATION	OUTCOME	TREATMENT	ORIGIN
1. Eppinger[13]	1890	M	52	Brain, lungs, pleura, and peribronchial nodes	Brain and meninges at autopsy	12 da.	Died	Aspiration of empyema	Germany
2. Ferre and Faquet[24]	1895	M	—	Brain	Brain at autopsy	—	Died	None	France
3. Sabrazes and Riviere[1]	1895	M	—	Brain, kidneys, and lungs	Organs at autopsy	—	Died	None	France
4. Sabrazes and Riviere[1]	1895	M	12	Lung; subcutaneous tissue	Sputum and abscesses	—	Died	None	France
5. Berestneff[25]	1897	—	—	Lungs and brain	Lungs and brain at autopsy	—	Died	None	Russia
6. Ljubimoff[26]	1897	—	—	Lungs	Lungs at autopsy	—	Died	None	Russia
7. Scheele and Petruschky[27]	1897	F	56	Lungs; subcutaneous tissues	Sputum and skin abscesses	7 mo.	Died	None	Poland
8. Buchholz[28]	1897	M	38	Lung	Lungs at autopsy	23 da.	Died	None	Germany
9. Flexner[29]	1898	M	70	Lung, peritoneum, and omentum	Lung at autopsy	—	Died	None	United States
10. Aoyama and Miyamoto[30]	1900	M	35	Brain and lungs	Sputum and lung abscesses	31 da.	Died	None	Japan
11. Musser[31]	1901	M	37	Lung	Lung at autopsy	3 mo.	Died	None	Philippine Islands
12. MacCallum[2]	1902	M	3	Peritoneum and liver capsule (postgastrostomy)	Peritoneal fluid	23 da.	Died	None	United States
13. Birt and Leishman[32]	1902	M	26	Lungs	Sputum, empyema fluid	6 mo.	Died	None	South Africa
14. Horst[33]	1903	M	33	Lungs, brain	Lung; brain	18 da.	Died	None	Germany
15. Schabad[34]	1904	M	62	Lungs, pericardium	Sputum; pleural fluid	3 yr.	Died	None	Russia

(Continued on next page.)

TABLE I.—CONT'D

REPORT	YEAR	SEX	AGE (YR.)	ORGANS INVOLVED	CULTURE	DURATION	OUTCOME	TREATMENT	ORIGIN
16. Stokes[3]	1904	M	28 da.	Lungs	Lung at autopsy	—	Died	None	United States
17. McDonald[35]	1904	F	65	Lungs; kidneys; brain; heart	Tissues at autopsy	6 mo.	Died	None	Scotland
18. Butterfield[36]	1904	M	19	Lungs	Lungs at autopsy	3 yr.	Died	None	United States
19. Loehlein[37]	1907	M	58	Lungs; brain; liver; spleen	Brain at autopsy	—	Died	None	Germany
20. Bernstein[38]	1907	M	67	Lungs; peritoneum	Lungs at autopsy	5 wk.	Died	Multiple paracenteses	England
21. Foulerton[19]	1910	M	55	Peritoneum	Peritoneal fluid at autopsy	24 da.	Died	None	England
22. Foulerton[19]	1910	M	50	Lungs	Lungs at autopsy	1 yr.	Died	None	England
23. Steele and Lee[39]	1913	M	19	Lungs	Sputum	6 mo.	Recovery	Thoracic drainage and bismuth paste	United States
24. Davis[40]	1914	M	64	Lungs	Sputum	4 wk.	Improved	Potassium iodide	United States
25. DeKorte[41]	1917	M	50	Ear; subcutaneous tissue	Aural and sinus exudates	3 yr.	Recovery	Iodides and autogenous vaccine	Africa
26. Henrici and Gardner[21]	1921	F	31	Lungs	Sputum	4 yr.	Improved		United States
27. Ribytkof and Maloletkof[42]	—	—	—	Spinal cord	Spinal cord at autopsy	—	Died	None	Russia
28. Jervell[43]	1921	M	20	Heart and spleen	Blood; vegetations from endocardium	3 wk.	Died	None	Sweden
29. Singer and Ballon[44]	1930	—	—	Lungs; kidneys; spleen; liver; adrenals; heart; skin	Sputum and skin abscesses	—	Died	None	United States
30. Holmer[45]	1931	M	57	Lungs and chest wall	Sputum and abscess of chest wall	20 mo.	Doing poorly	Intravenous iodides	United States
31. Monserrat[4]	1932	M	4 Mo.	Lungs; subcutaneous tissues; skin	Lung at autopsy	3 mo.	Died	None	Philippine Islands

32. Freed and Light[46]	1932	M	39	Lungs; liver; heart; skin; bone	Blood cultures and organs at autopsy	30 mo.	Died	Iodides; drainage of empyema and abcesses of skin and bone	United States
33. Guy and Helmbold[47]	1933	F	36	Skin; subcutaneous tissues and bone	Blood culture; abscesses of skin and bone	10 mo.	Improved	Iodides	United States
34. Fairley and Mackie[48]	1935	M	60	Skin and subcutaneous tissue; liver; spleen; pancreas and colon	Subcutaneous tissues and liver at autopsy	3 mo.	Died	None	England
35. Alestra and Girolami[49]	1937	M	18	Heart	Endocardial vegetations and blood	—	Died	Iodides	Poland
36. Alestra and Girolami[49]	1937	M	37	Heart (endocardium)	Endocardial vegetations at autopsy	5 mo.	Died	Iodides; sulfanilamide; Prontosil	Poland
37. Goldsworthy[50]	1937	M	69	Lungs; kidneys; adrenals; subcutaneous tissue	Sputum	1 mo.	Died	None	Australia
38. Kessel and Goolden[51]	1938	F	—	Lungs and meninges	Lungs and meninges at autopsy	—	Died	None	United States
39. Benbow et al.[52]	1944	M	52	Lungs; brain; chest wall; perirectal area	Sputum	13 mo.	Recovered	Sulfathiazole, sulfadiazine, iodides, x-ray, and surgery	United States
40. Benbow et al.[52]	1944	F	36	Lungs; subcutaneous tissue	Sputum and subcutaneus abscess	13 mo.	Recovered	Sulfanilamide, iodides, x-ray, and surgery	United States
41. Binford and Lane[53]	1945	M	51	Lungs; brain; ischiorectal area	Involved tissues at autopsy	6 wk.	Died	None	United States
42. Kirby and McNaught[22]	1946	M	63	Lungs; spleen; thyroid; subcutaneous tissue; ileum and kidneys	Blood and sputum	4 mo.	Died	Sulfadiazine and x-ray	United States
43. Kirby and McNaught[22]	1946	F	49	Brain	Brain at autopsy	1 mo.	Died	None	United States

(Continued on next page.)

TABLE I.—CONT'D

REPORT	YEAR	SEX	AGE (YR.)	ORGANS INVOLVED	CULTURE	DURATION	OUTCOME	TREATMENT	ORIGIN
44. Shaw, et al.[54]	1946	F	34	Lungs; subcutaneous tissue	Pleural fluid	16 mo.	Recovered	Sulfadiazine, penicillin, iodides, thymol, and surgical drainage	United States
45. Calero[5]	1946	F	12	Lungs	Sputum and pleural fluid	7 mo.	Recovered	Sulfadiazine and penicillin	Panama
46. Wedding[55]	1947	M	37	Heart (endocardium and myocardium); spleen; kidney	Blood and endocardial vegetations	2 yr.	Died	Sulfathiazole and sulfadiazine	United States
47. Wedding[55]	1947	F	71	Heart (endocardium)	Endocardial vegetations at autopsy	—	Died	None	United States
48. Glover et al.[56]	1948	M	26	Lungs	Empyema fluid	4 yr.	Recovered	Sulfadiazine, penicillin, and streptomycin	United States
49. Schafer[57]	1948	M	28	Lungs	Sputum	5 mo.	Recovered	Sulfadiazine and penicillin	United States
50. Buchanan et al.[58]	1948	—	—	Ears and subcutaneous tissues	Aural and sinus exudates	—	Recovered	Iodides	Africa
51. Buchanan et al.[58]	1948	F	—	Lungs; heart (pericardium); peritoneum and skin	Involved organs at autopsy	1 mo.	Died	Iodides	Africa
52. Buchanan et al.[58]	1948	M	—	Lungs and skin	Sputum; lungs	1 mo.	Died	None	Africa
53. Buchanan et al.[58]	1948	M	—	Lungs	Empyema fluid	3 mo.	Died	Surgical drainage of empyema	Africa
54. Buchanan et al.[58]	1948	M	—	Lungs; chest wall	Empyema fluid at autopsy	2 mo.	Died	None	Africa
55. Buchanan et al.[58]	1948	M	—	Lungs and pleura	Sputum and pleural fluid (also had Tbc.)	1 yr.	Not known	None	Africa
56. Tucker and Hirsch[59]	1949	M	39	Skin and brain	Skin and brain abscesses	—	Died	Sulfadiazine, penicillin, streptomycin	United States
57. Tucker and Hirsch[59]	1949	M	30	Lungs; skin; lymph-nodes	Lungs and nodes at autopsy	6 mo.	Died	Sulfadiazine, penicillin, streptomycin	United States

58. Tucker and Hirsch[59]	1949	F	23	Skin and bone	Exudate from skin and mandible	1 mo.	Not known	Sulfadiazine, penicillin, streptomycin	
59. Hager et al.[60]	1949	F	16	Lungs	Empyema fluid	3 mo.	Recovered	Penicillin, streptomycin, sulfadiazine, and surgical drainage	United States
60. Hager et al.[60]	1949	F	64	Lungs	Sputum	3 yr.	Not known	Penicillin, streptomycin, sulfadiazine	United States
61. Cuttino and McCabe[6]	1949	F	3	Lymph nodes; liver; spleen and colon	Nodes at surgery; organs at autopsy	3 mo.	Died	Penicillin and x-ray	United States
62. Eckhardt and Pilcher[61]	1950	F	50	Brain	Brain abscess	1 yr.	Died	Surgical drainage of brain abscess	United States
63. Mogabgab and Floyd[62]	1951	F	31	Lungs and bronchi	Sputum	9 mo.	Unknown	Penicillin	United States
64. Connar et al.[63]	1951	M	37	Lungs	Sputum and empyema fluid	7 mo.	Recovery	Penicillin, streptomycin, and surgery	United States
65. Kohn et al.[64]	1951	M	50	Lungs	Blood	4 mo.	Recovery	Penicillin, streptomycin, Terramycin, sulfadiazine, and iodides.	United States
66. Bernstein et al.[65]	1952	M	39	Lungs; pleura; kidneys; subcutaneous tissue; meninges	Skin and lung abscesses and meningeal exudate	3 mo.	Died	Penicillin, streptomycin, and Aureomycin	United States
67. Bernstein et al.[65]	1952	M	60	Lungs; pleura; brain	Pleural fluid and brain abscess at autopsy	4 mo.	Died	Penicillin, streptomycin, and Aureomycin	United States
68. Bernstein et al.[65]	1952	F	23	Lungs	Pleural fluid	4 da.	Recovered	Penicillin and streptomycin	United States
69. Cruz and Clancy[66]	1952	F	43	Bone; heart; brain; kidney; adrenals; lymph nodes	Involved tissue at autopsy	—	Died	Neomycin and Terramycin	United States

(Continued on next page.)

TABLE I.—CONT'D

REPORT	YEAR	SEX	AGE (YR.)	ORGANS INVOLVED	CULTURE	DURATION	OUTCOME	TREATMENT	ORIGIN
70. Kaufman and Prieto[67]	1952	M	53	Lungs; brain; pancreas; lymph nodes	Brain abscess	15 da.	Died	Penicillin, Aureomycin, sulfadiazine, and surgery	United States
71. DeUrioste and Medarde[68]	1953	M	—	Lungs and skin	Sputum; skin abscess	4 mo.	Died	Not known	Spain
72. DeUrioste and Medarde[68]	1953	M	—	Lungs and skin	Skin abscesses	4 mo.	Died	Not known	Spain
73. O'Reilly and Powell[69]	1953	M	44	Brain	Brain at autopsy	23 da.	Died	None	Australia
74. Wichelhausen et al.[23]	1954	M	35	Lungs; brain; chest wall, and skin	Brain abscess	15 mo.	Died	Penicillin, streptomycin, Chloromycetin, Gantrisin, sulfadiazine, and surgery	United States
75. Krueger et al.[70]	1954	M	42	Lungs and brain	Sputum; brain abscess	4 da.	Recovery	Penicillin, Aureomycin, streptomycin, Terramycin, and surgery	United States
76. Turner[7]	1954	M	15	Brain; meninges; lymph nodes	Brain abscess	6 mo.	Died	Penicillin, triple-sulfa, Terramycin, and surgery	United States
77. Turner[7]	1954	M	31	Brain	Brain abscess at autopsy	2 wk.	Died	None	United States
78. Hunter et al.[71]	1954	F	50	Lungs; kidneys; liver; spleen, and veins	Involved tissue at autopsy	1 yr.	Died	Penicillin, streptomycin, and sulfamethazine	England
79. List et al.[72]	1954	M	48	Brain and lungs	Brain abscess	5 mo.	Recovered	Penicillin, Aureomycin, streptomycin, and surgery	United States
80. Munslow[73]	1954	M	22	Brain	Brain abscess †	7 mo.	Recovered	Penicillin, streptomycin, and surgery	United States
81. Moore et al.[74]	1954	M	49	Skin and knee joint	Synovial exudate	—	Recovered	Surgery	United States
82. Weed et al.[8]	1954	M	15 mo.	Lungs; pancreas; brain; chest wall	Involved tissues at autopsy	3 mo.	Died	Terramycin, Aureomycin, penicillin, and cortisone	United States

83. Kurowska-Taylorwa and Majewski[9]	1954	F	4	Gastrointestinal tract	Involved tissues	—	Not known	Terramycin, Aureomycin, penicillin	Poland
84. Bobbitt et al.[75]	1955	M	50	Skin; lungs and muscle	Lung and psoas muscle abscesses	2 mo.	Died	Penicillin	United States
85. Bobbitt et al.[75]	1955	F	55	Skin and brain	Involved tissues at operation	3 da.	Recovery	Penicillin, sulfadiazine, choloramphenicol, and surgery	United States
86. Bobbitt et al.[75]	1955	M	61	Lungs	Lung abscesses	8 mo.	Recovery	Penicillin, Benamid, surgery, and sulfadiazine	United States
87. Clapp and Williams[76]	1955	M	28	Lungs and brain	Sputum and brain at autopsy	15 mo.	Died	Sulfadiazine and actidione	United States
88. Clapp and Williams[76]	1955	M	29	Lungs; thyroid; and retroperitoneal tissues	Blood; involved tissues at autopsy	9 mo.	Died	Penicillin	United States
89. Rankin and Javid[10]	1955	F	13	Brain	Brain abscess	1 yr.	—	Penicillin, triple-sulfa, Aureomycin, and streptomycin	United States
90. Weed et al.[11]	1955	M	26	Lungs and pleura	Pleural fluid	2 yr.	Recovered	Sulfadiazine	United States
91. Weed et al.[11]	1955	M	7	Lungs	Lungs at autopsy	3 mo.	Died	Penicillin	United States
92. Weed et al.[11]	1955	M	42	Lungs	Sputum	11 mo.	Died	Sulfadizine	United States
93. Weed et al.[11]	1955	F	57	Lungs; spleen; peritoneum	Lungs at autopsy	9 mo.	Died	Streptomycin, urethane, PASA	United States
94. Weed et al.[11]	1955	F	57	Lungs and brain	Tissues at autopsy	10 mo.	Died	Unknown	United States
95. Weed et al.[11]	1955	F	53	Lungs and brain	Bronchial secretion and brain abscess	11 mo.	Died	Penicillin, streptomycin, and sulfadiazine	United States

TABLE II. FREQUENCY OF THE INVOLVEMENT OF THE VARIOUS ORGANS IN THE NINETY-FIVE REPORTED CASES OF NOCARDIOSIS

ORGAN INVOLVED	NUMBER OF CASES
Lungs	67
Brain	29
Skin and subcutaneous tissues	29
Pleura	15
Heart	11
Kidneys	9
Spleen	9
Liver	7
Peritoneum	7
Lymph nodes	7
Bone	5
Pancreas	4
Meninges	4
Small and large bowel	4
Adrenal gland	3
Thyroid gland	2
Spinal cord	1

represent primary pulmonary infections, the lungs having been involved in more than two-thirds of the cases. Involvement of the brain, skin, and subcutaneous tissues stands next in frequency, as shown in Table II. The disease has been diagnosed only at autopsy in thirty-eight instances. There have been sixty-five deaths, a mortality rate of 68.4 per cent. Twenty patients have recovered, and the outcome is not known in ten cases. Fifty per cent of the fatal cases received no therapy. There has been only a slight decline in the mortality rate since the advent of the sulfonamide drugs and antibiotics.

Although nine species of Nocardia have been identified, only three species have been shown to be pathogenic for man (Table III). *Nocardia asteroides* has been the infectious agent in all but a few of the recorded cases. *Nocardia brasiliensis* is a known pathogen in Central and South America but has also been reported from the United States.[74, 75] *Nocardia intracellularis*, the third pathogen, is an obligate intracellular parasite which was isolated from the lymph nodes, spleen, liver, and colon of a 34-month-old child by Cuttino and McCabe.[6]

Nocardia appears in stained smears of fresh sputum and exudate as gram-positive, weakly acid-fast or nonacid-fast, single or branching filamentous rods. The organism fragments readily into bacillary and coccal forms; the former may be indistinguishable from tubercle bacilli. The coccal and coccobacillary forms are frequently confused with diphtheroid organisms.[23, 48, 54, 65, 77] The acid-fastness is most readily seen in early milk cultures and tends to disappear after repeated transfers

TABLE III. CLASSIFICATION OF THE PATHOGENIC FORMS OF ACTINOMYCETES

ORDER ACTINOMYCETALES	
I. Mycelium rudimentary or absent (Family *Mycobacteriaceae*)	
A. Acid-fast organisms	*Mycobacterium*
II. True mycelium produced:	
A. Vegetative mycelium fragments into bacillary and coccoid elements (Family *Actinomycetaceae*)	
1. Anaerobic or microaerophilic, parasitic, and nonacid-fast organisms	*Actinomyces*
2. Aerobic, partially acid-fast or nonacid-fast organisms	*Nocardia*
B. Vegetative mycelium not fragmented into bacillary or coccoid elements (Family *Streptomycetaceae*)	
1. Multiplication by conidia in chains from arial hyphae	*Streptomyces*
2. Multiplication by single terminal spore or short sporophores	*Micromonospora*

on artificial media.[60] Acid-alcohol decolorization may fail to demonstrate acid-fastness, but it can occasionally be shown when a 1 per cent solution of sulfuric acid is utilized.[22, 60] This property is usually more pronounced in tissues than it is in cultural material. The usual concentration of sodium hydroxide (3 to 4 per cent) used in concentrating tubercle bacilli destroys Nocardia.[22, 60, 65]

The organism grows well on ordinary media under aerobic, preferably alkaline, conditions at 20° to 37° C. Growth over a wide temperature range (−7° to 55° C.) has been demonstrated and is considered as a factor supporting the belief that these organisms are common inhabitants of the soil.[60] Mycelial, ball-like colonies usually appear in twenty-four to seventy-two hours, but four to six weeks may be required for recognizable growth. The colonies assume a glabrous star-shaped appearance, being moist and mucilaginous or dry and of the consistency of tubercle bacilli. Colonies are chromogenic, appearing cream to orange in color. The color is related to heat and light, being deepest in the presence of light and at temperatures below 30° C.[69] With aging they assume a wrinkled appearance due to an overgrowth of mycelia and may become gram-negative. At high temperatures the colonies become more bacterium-like due to the inhibition of mycelial production. The colonies form dry, wrinkled pellicles on the surface of liquid media. Nocardiae do not ferment carbohydrates, form indol, H_2S, or NH_3. The peptonization of milk, liquefaction of gelatin, and coagulation of milk show species and strain variation. Their growth can be supported by simple hydrocarbons such as paraffin.[65] In tissues and exudates the organisms may form fine granules which are easily distinguished from those of *Actinomyces bovis* by the absence of clubs. Hematoxylin and eosin fail to stain the organism but it is readily demonstrated with Gram stain or with MacManus' PAS stain. The life cycle and morphology of Nocardia are well described.[78-80] The organism begins as a microcyst which germinates by budding to form multinucleate and multicellular filaments. Multiplication of the cells takes place by simple fission, by budding, or by a complex vegetative reproduction.[79]

Biagi[81] reported the first serological investigation of the aerobic actinomycetes in 1904, demonstrating cross-agglutination between five species. Slack and associates[82] have shown cross-agglutination between Streptomyces, Nocardia, and Mycobacterium. In addition to the well-known cultural and morphological similarities between Nocardia and Mycobacterium, there is a close antigenic relationship as shown by cross-agglutination and cross-complement fixation.[83-85] *N. asteroides* is more closely related to the tubercle bacillus than to *A. bovis* as indicated by immunological and pathogenic characteristics.[85, 86] Nocardia replaces the tubercle bacillus as an adjuvant in the production of skin sensitization to pieryl chloride and in the production of isoallergic meningoencephalitis.[87] An oil emulsion of killed *N. asteroides* induces a delayed type of sensitivity to an extract of the fungus, and has been shown to sensitize guinea pigs to tuberculin.[87, 88] Other investigators, however, have pre-

pared skin test material with both protein and polysaccharide extracts of the organism and have shown the allergens to be thermolabile and specific. They found that five to six weeks were required for sensitization; positive skin tests occurred in twenty-four to forty-eight hours and often persisted for seven days. Although agglutinins, complement-fixing antibodies, and precipitins have been demonstrated in the experimental infection, they have never been demonstrated in man. Positive skin tests, however, have been shown in both *N. asteroides*[56] and *N. brasiliensis* infections in man.[89]

It is interesting that several antibiotics have been isolated from Nocardia.[90] A water-soluble tuberculostatic substance referred to as Nocardin has been shown to be as effective as streptomycin in the suppression of experimental tuberculosis in mice.[91] Nocardia has further been shown to have a bacteriolytic action on living *Staphylococcus aureus*.[92] All antibacterial substances isolated from Nocardia to date have been shown to be too toxic for clinical use.[90, 91]

The incidence of nocardial infections is unknown although it is probably higher than is generally recognized. The saprophytic nature of the organism, its low-grade pathogenicity, and its sensitivity to multiple antibiotics and chemotherapeutic agents would tend to give a definite incidence of inapparent and clinically undiagnosed infections. In support of this view is the fact that most of the reported cases have been diagnosed only at autopsy or in the terminal stage of the disease. Nocardiae, unlike Actinomyces, are free-living in nature. They have been shown to be widely distributed in the soil and on plants and grasses.[93] They have been reported as air-borne laboratory contaminants[21] and as contaminants of the skin of healthy laboratory animals.[94] There is no evidence that they are facultative parasites of man. However, they have been cultured from the urine of patients with symptoms of transient cystitis where their pathologic significance was doubted[95] and have been reported in the surgically-excised spleen of patients with acholuric jaundice as incidental findings.[96] Nocardiosis has been reported in dogs,[97-102] cats,[103] and marsupials.[104] There is no good evidence for animal to man or man to man transmission. The high incidence of primary pulmonary infections points to the respiratory tract as the usual site of entry; however the gastrointestinal tract has been shown to be a portal for the disease in man.[59, 61, 105] The organism may also be introduced into the tissues through superficial trauma. The geographical distribution of the infection is world-wide; it occurs in all races and occupations. Males have been affected twice as commonly as females. The disease has been reported in age groups from 4 weeks to 70 years.

The lungs are primarily or secondarily involved in most cases. The pathology is that of a caseous-like bronchopneumonia with subsequent suppuration and occasional cavitation. True caseation does not occur. There is a tendency for hematogenous dissemination with metastatic abscess formation in multiple organs. Extension to the pleura, with empyema formation, is relatively frequent.

The microscopic picture varies from one of suppuration to that of granulomatous lesions resembling tuberculosis. Giant cells are occasionally present but tubercle formation does not occur.[8, 11, 22, 106] The basic histological lesion is a focus of necrosis surrounded by a variable cellular infiltrate. This is frequently surrounded by a peripheral zone of granulation tissue composed of mononuclear phagocytes. The absence of encapsulation of abscesses is characteristic, and secondary fibrosis may be minimal to absent[8, 11, 22] or may be extensive.[106] The tendency for extension and spread is variable. Lesions have been reported which suggest fifteen years of localized disease.[22, 54] Secondary amyloidosis has not been reported. Gram-positive and occasionally acid-fast, filamentous, branching, bacillary forms of the organism are scattered throughout the involved tissues.

The literature on animal pathogenicity is conflicting.[60, 86, 93, 107] The results vary from no illness at all to an acutely disseminated infection and death. The organism is inconstantly pathogenic for rabbits and guinea pigs. Intravenous or intraperitoneal inoculation of animals may give localized or disseminated disease and intramuscular inoculation results in localized abscess formation.

The clinical picture of nocardiosis may be that of an acute or chronic pulmonary disease, a chronic suppurative disease of the skin, subcutaneous tissues and bone, a primary disease of the central nervous system, or a widely disseminated infection with multiple systems involvement.

The disease is most frequently manifest as an acute or chronic pulmonary disease, with a tendency to suppuration, empyema formation, and hematogenous dissemination. The most common symptoms are cough, fever, anorexia, weight loss, malaise, night sweats, fatigue, dyspnea, and chest pain; hemoptysis is uncommon. The disease shows a tendency to chronicity with remissions and exacerbations. The duration of the clinical course in the reported cases varies from a few days to four years. Pulmonary lesions may remain quiescent and asymptomatic for four to twelve months.[11, 46, 54] Roentgenological findings in the lungs are nonspecific and may simulate bacterial pneumonias and any of the common infectious granulomas. The clinical picture may be that of a brain abscess or a purulent meningitis. There are numerous reports in the literature of primary brain abscess due to Nocardia.[7, 10, 61, 70] Other clinical and pathological pictures described include peritonitis,[19, 20, 58, 65] pericarditis,[34, 54, 58] osteitis,[46, 47, 59, 66] arthritis,[74] endocarditis,[43, 49, 55, 66] pancreatitis,[48, 67] pylephlebitis,[48, 71] retroperitoneal tumor,[6, 76] tracheitis and bronchitis,[45, 59, 62, 63] pleurisy,[45] pleuropulmonary fistula,[5, 46] ischiorectal and perirectal abscess,[52, 53] psoas muscle abscess,[22, 75] appendiceal abscess,[46] otomycosis,[58, 73] and chronic keratoconjunctivitis.[108] Hepatomegaly, splenomegaly, signs of increased intracranial pressure, and urinary symptoms are usually manifestations of widely disseminated disease.

The diagnosis of nocardiosis is based upon the recovery of the organism from the blood, sputum, or exudate. Other laboratory aids are of little

value in the diagnosis. A moderate to marked leukocytosis and an associated anemia are constant findings in the reported cases and may be of value in the differential diagnosis. Since the organism is a free-living saprophyte in nature, a positive sputum is by no means diagnostic. A high index of suspicion and repeated cultures of appropriate material are usually necessary to establish the diagnosis. Pathogenic fungi are usually resistant to antibiotic and chemotherapeutic agents, and, for this reason, as in the case reported here, there is a tendency to attempt cultivation of the organism while the patient is on therapy. Nocardia, however, is sensitive to multiple antibiotic and chemotherapeutic agents, and, though clinically ineffective, they may interfere with cultural detection.[23] Biopsy of the lung, liver, or lymph nodes may be necessary for the diagnosis at times.

Nocardia is a frequently reported etiological factor in cases of pulmonary disease simulating tuberculosis. The literature demonstrates how closely the clinical and pathological picture can parallel both chronic pulmonary tuberculosis and acute miliary and disseminated forms of tuberculosis.[11, 38, 45, 46, 56, 62, 63, 65, 68, 71] The patients of many of the reported cases have been treated for tuberculosis. A 5 per cent incidence of nocardial infections in a tuberculosis sanatorium is cited by one author.[108] The simultaneous occurrence of nocardiosis and tuberculosis has been shown in at least two of the reported cases.[11, 58] Other diseases to be considered in the differential diagnosis include actinomycosis, sarcoidosis, histoplasmosis, coccidiomycosis, cryptococcosis, sporotrichosis, lymphomas, carcinoma, syphilis, collagen disease, the reticuloendothelioses, tularemia, Klebsiella pneumonia, and other pyogenic pneumonias. The disease must be suspected in all chronic suppurative conditions, in all obscure pulmonary infections not responding to antibiotics, and in all cases of tuberculosis where the bacteriological diagnosis is lacking.

The mortality rate in the recognized cases is high but, as has been pointed out,[23] the frequency with which the diagnosis is made only at autopsy or in the terminal phase of the disease suggests that subclinical infections may be frequent. The survival rate in this infection seems to be directly related to early bacteriological diagnosis and the institution of appropriate therapy.

Prior to the use of the sulfonamide drugs and antibiotics, thymol and iodides were the usual therapeutic agents and their ineffectiveness is apparent in the literature. Nocardia has been shown to be inhibited in vitro by fourteen different antibiotic and chemotherapeutic agents.[109] Streptomycin, Aureomycin, Terramycin, and chloramphenicol have been shown to lengthen the survival time of experimental animals.[109] In in vitro studies of twenty-six strains of Nocardia, one investigator found the sulfonamide drugs to be the agents of choice.[23] Sulfadiazine is the only drug shown to be 100 per cent effective in experimental nocardial infections.[109] The in vitro studies of other investigators confirm the efficacy of the sulfonamides.[60, 110, 111] The development of in vitro resistance to streptomycin and penicillin has been demonstrated.[112] Actidione[76] and

para-aminobenzoic acid[113] have been shown to be ineffective while pregnenolone acetate[114] and penicillin[111] have been shown to be somewhat effective.

In support of these laboratory studies is the fact that most of the reported recoveries in nocardiosis have received sulfonamide drugs, either alone or in combination with antibiotics and surgical drainage. The fatal cases in the literature which received the sulfonamide drugs cannot be interpreted as failures of therapy, for, in most instances, the drugs were administered for only a brief period or only in the terminal stage of the disease. It would appear, therefore, that the treatment of choice in this infection is the sulfonamide drugs combined with appropriate surgical drainage.

DISCUSSION

The resemblance between J. F.'s clinical picture and that associated with the reported cases of nocardiosis is striking in that this patient, too, showed an unrelenting fever, growth failure, anemia, clinical and roentgenological evidence of remissions and exacerbations, and a lack of response to antibiotics. The close resemblance to tuberculosis in its manifestations was conspicuous in this patient as it usually is in patients with nocardiosis. In view of the reported efficacy of the sulfonamide drugs in the treatment of nocardial infections, it is interesting to note that the patient showed an apparent response to the administration of these agents on several occasions during the course of his illness (Figs. 2 and 3). A question which must be raised is whether the disease represents a primary nocardial infection or a secondary complication due to the extensive utilization of antibiotics. In view of the clinical course, roentgenological findings, and pathology, it is felt that the patient represents a case of chronic nocardial infection. The isolation of acid-fast organisms resembling tubercle bacilli suggests the possibility of the coexistence of tuberculosis and nocardial infection.

SUMMARY

1. A fatal case of nocardiosis, clinically simulating tuberculosis, in a 45-month-old male is presented. This represents the twelfth reported case of nocardiosis in the pediatric age group.

2. The bacteriology, clinical features, pathology, and treatment of nocardial infections are reviewed.

3. The morphological, cultural, biochemical, antigenic, and pathogenic similarities of Nocardia and the tubercle bacillus are emphasized.

4. Nocardia may become predominant and invasive as a result of prolonged antibiotic therapy.

5. The saprophytic nature of the organism, its low grade pathogenicity for man, and its in vitro sensitivity to multiple antibiotics and chemotherapeutic agents are pointed to as factors which probably give a significant incidence of clinically inapparent infections.

6. Nocardia is sensitive in vitro to multiple antibiotics and, although clinically ineffective, these agents may interfere with cultural detection of the organism.

7. It is suggested that the disease be considered in all chronic suppurative disease, in all cases of obscure

bronchopulmonary disease unresponsive to antibiotics, and in all cases of suspected tuberculosis where a bacteriological diagnosis is lacking.

8. The diagnosis of nocardiosis is bacteriological. The survival rate is related to early diagnosis and institution of appropriate therapy. Sulfonamide drugs, alone or in combination with penicillin and appropriate surgery, represent the treatment of choice.

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Juvenile Delinquency, Vintage of 1757

Whereas Complaint has been made to the Selectmen that the Children behave very unmannerly & Indescently in the Streets & use bad Language, Voted That the Masters of the respective Schools in the Town be desired to reprove Said Children for Such Misdemeanors.

MINUTES OF BOSTON SELECTMEN, January 19, 1757.

THE EFFECT OF CORTICOTROPIN ON THE ACTIVITY OF THE ADRENAL CORTEX OF THE MALE CHILD

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IN A recent publication[1] we reported a study of the effect of corticotropin on the adrenocortical activity of the newborn male infant, and observed a positive response in thirteen of twenty-three male infants 1 to 5 days of age. An increase of over 20 per cent in the excretion of the total neutral 17-ketosteroids after the administration of corticotropin was utilized as the criterion of a positive response. It was decided to extend this investigation to older children so that the effect of age on the response of the adrenal cortex to corticotropin might be observed.

METHODS

Thirty-seven children up to 11 years of age, including eight controls, partook in this study. The infants studied were selected from the newborn nurseries. They were males, born at term, who showed normal growth and development during their neonatal stay. The older children were chosen from those admitted to the pediatric ward for various minor infections. All the children selected had recovered completely from their ailment, and presented no fever or any evidence of organic disturbance at the time of observation for this study.

For the sake of convenience, urine specimens were collected from 10 P.M. to 6 P.M. Twenty-four or forty-eight hours later at 10 P.M., one unit of corticotropin in gelatin solution per kilogram of body weight was administered intramuscularly. Where the child was too young to signify a desire to urinate, a tubing procedure previously described[1] was employed. In the case of the controls, the above procedure was likewise followed, except that no corticotropin was administered.

Sodium, potassium, 17-ketosteroid, and 17-hydroxycorticoid determinations were performed on all urine samples. Sodium and potassium were determined by flame photometry. 17-Ketosteroids were determined by a modification of the method of Zimmerman and co-workers.[2, 3] For the 17-hydroxycorticoids the method of Reddy and associates[4] was employed.

RESULTS AND DISCUSSION

All results are listed in Table I. Of the eight controls studied, none showed an increase of more than 25 per cent in the excretion of 17-ketosteroids and 17-hydroxycorticoids in successive samples. Therefore, a positive response to corticotropin was considered to have occurred when a 50 per cent increase was obtained in the excretion of either the 17-ketosteroids or the 17-hydroxycorticoids. Twenty-four of the twenty-nine children studied responded to corticotropin according to the criteria listed

From the Biochemistry Department and the Pediatric Department of Bridgeport Hospital.

TABLE I. A COMPARISON OF THE URINARY SODIUM, POTASSIUM, 17-KETOSTEROIDS, AND 17-HYDROXYCORTICOIDS BEFORE AND AFTER THE ADMINISTRATION OF CORTICOTROPIN

		BEFORE CORTICOTROPIN					AFTER CORTICOTROPIN (1 UNIT PER KG. OF BODY WEIGHT)					
CHILD	AGE	URINE VOLUME (ML.)	URINARY NA (MG. EXCRETED 10 P.M.-6 A.M.)	URINARY K (MG. EXCRETED 10 P.M.-6 A.M.)	17-KETOSTEROIDS (MG. EXCRETED 10 P.M.-6 A.M.)	17-HYDROXYCORTICOIDS (MG. EXCRETED 10 P.M.-6 A.M.)	URINE VOLUME (ML.)	URINARY NA (MG. EXCRETED 10 P.M.-6 A.M.)	URINARY K (MG. EXCRETED 10 P.M.-6 A.M.)	17-KETOSTEROIDS (MG. EXCRETED 10 P.M.-6 A.M.)	17-HYDROXYCORTICOIDS (MG. EXCRETED 10 P.M.-6 A.M.)	RESPONSE TO CORTICOTROPIN
Ch	1 da.	20	11.2	24.4	0.90	1.30	24	8.4	31.7	0.54	0.94	–
W	1 da.	34	6.8	38.0	1.00	0.57	68	7.5	57.0	0.68	0.86	+
P	2 da.	35	5.3	17.8	0.33	0.29	48	7.4	36.5	0.80	0.65	+
F	3 da.	21	23.1	18.9	0.60	0.57	28	19.0	19.0	0.58	0.64	–
Cu	3 da.	95	8.8	44.0	0.62	1.22	215	20.4	99.3	0.92	2.08	+
M	7 da.	136	57.1	68.0	1.24	0.94	100	1.0	110.0	1.08	1.42	+
H	9 da.	100	100.0	80.0	0.55	0.77	120	81.6	120.0	0.63	0.76	–
St	2 mo.	130	117.0	455.0	0.81	2.20	180	106.0	342.0	0.99	2.40	–
E	2 mo.	100	134.0	180.0	0.37	0.65	68	74.8	156.0	0.55	1.15	+
R	2 mo.	45	9.5	122.0	0.66	1.01	90	16.0	108.0	0.71	1.40	–
D	3 mo.	83	166.0	207.0	0.31	0.90	58	35.0	371.0	0.60	0.93	+
K	10 mo.	46	41.0	145.0	0.71	0.82	75	85.5	182.0	0.58	1.21	+
S	10 mo.	164	266.0	476.0	1.02	0.20	155	217.0	464.0	1.18	0.69	+
Tr	15 mo.	90	131.0	306.0	0.71	0.29	110	143.0	561.0	1.14	1.14	+
H	22 mo.	66	152.0	297.0	0.75	0.53	72	302.0	482.0	0.80	1.22	+
Pl	2 yr.	42	123.0	235.0	0.44	1.18	66	330.0	475.0	0.92	2.22	+
C	2 yr.	63	222.0	233.0	0.54	0.18	32	750.0	180.0	0.49	0.32	+
Y	2 yr.	100	440.0	340.0	0.66	0.11	300	720.0	780.0	1.67	1.10	+
Ti	5 yr.	154	477.0	314.0	1.04	0.38	156	187.0	811.0	1.28	2.20	+
Re	5 yr.	240	115.0	250.0	3.70	0.36	160	185.0	704.0	1.74	3.40	+
Pr	7 yr.	155	186.0	512.0	1.50	0.14	100	157.0	410.0	0.78	1.60	+
Da	7 yr.	240	226.0	552.0	1.95	0.76	255	219.0	1887.0	2.14	2.90	+
B	9 yr.	300	186.0	339.0	1.60	0.40	130	190.0	416.0	2.10	1.40	+
A	9 yr.	146	263.0	438.0	1.04	0.74	118	590.0	336.0	1.18	3.10	+
Ch	9 yr.	205	615.0	267.0	1.50	0.16	400	524.0	480.0	2.10	0.91	+
Pu	10 yr.	250	610.0	750.0	1.90	0.27	164	190.0	984.0	2.21	3.53	+
Ra	11 yr.	210	186.0	525.0	1.86	0.69	78	390.0	351.0	1.70	5.00	+
Ad	11 yr.	430	1230.0	1204.0	3.80	1.00	110	264.0	800.0	1.93	2.20	+
Cr	11 yr.	320	314.0	416.0	1.66	2.56	240	360.0	1152.0	2.40	4.10	+
		NO CORTICOTROPIN ADMINISTERED										
Th	2 da.	42	98.7	34.0	0.83	0.35	65	107.0	42.2	0.67	0.43	
So	3 da.	39	39.6	25.2	0.60	0.23	110	74.6	30.8	0.74	0.28	
Ka	10 yr.	100	35.0	140.0	1.30	2.21	120	123.0	175.0	1.31	1.59	
Ro	2 da.	37	2.5	26.2	0.61	0.49	46	4.5	35.4	0.60	0.42	
Ri	6 yr.	100	344.0	300.0	0.96	0.71	117	386.0	205.0	1.11	0.84	
K	11 yr.	95	342.0	234.0	1.22	2.16	175	1012.0	368.0	1.03	2.00	
Re	6 yr.	155	93.0	370.0	1.00	1.15	160	150.0	397.0	0.89	0.93	
Fo	4 yr.	75	201.0	278.0	0.79	0.82	85	270.0	300.0	0.73	0.88	

above. In only two of these twenty-four cases were the 17-hydroxycorticoids not elevated. However, an elevation in the 17-ketosteroids occurred in only nine of the twenty-four cases. This indicates that the urinary 17-hydroxycorticoids are a more sensitive index to adrenocortical response after corticotropin administration than are the 17-ketosteroids.

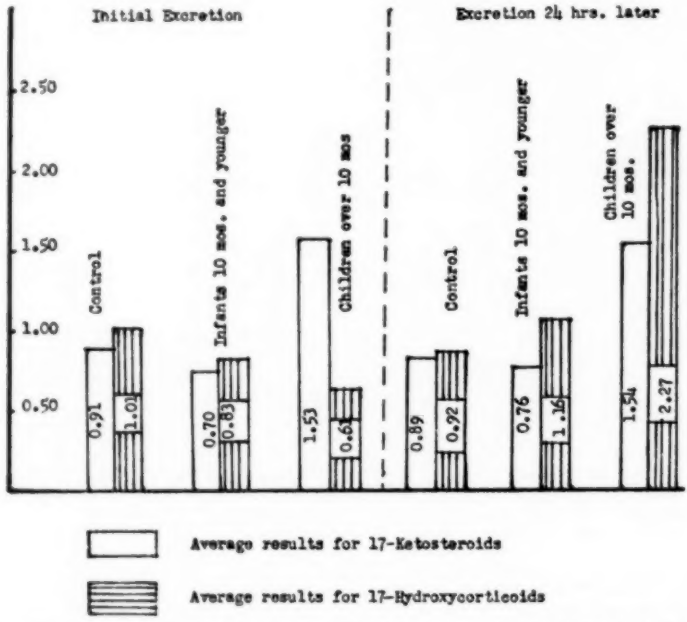

Fig. 1.—Averaged results for 17-ketosteroids and 17-hydroxycorticoids in the control group, in the infants 10 months and younger, and in the children over 10 months.

The five children that did not respond to corticotropin were all under 3 months of age. Eight male infants in that same age group and all the children older than 10 months showed a positive response to corticotropin. In the age group 2 days to 3 months, those children who showed a positive response to corticotropin did not reveal a marked increase in the excretion of the 17-hydroxycorticoids, the increase averaging about 75 per cent. In children older than 10 months, the increase in the excretion of the urinary 17-hydroxycorticoids is much greater, averaging several hundred per cent. The increase in the urinary 17-ketosteroids is likewise more marked in the older age group. Therefore, it would appear that an increase in the physiological activity of the adrenal cortex occurs within the first year of life, as indicated by an increased response of the adrenal cortex to corticotropin. After the first year of life, the response of the adrenal cortex to corticotropin has become close to maximal so far as the excretion of 17-hydroxycorticoids is concerned. This would suggest that during the early months of life, the adrenal cortex has not yet reached a

state of maximum responsitivity. These results are depicted graphically in Fig. 1.

So far as the urinary excretion of sodium and potassium is concerned, the results obtained in the controls in successive samples collected within twenty-four hours were not consistent. They varied considerably, even though dietary factors were controlled as closely as possible. Consequently, because of this variation, no attempt was made to interpret the change in the urinary excretion of sodium and potassium after the administration of corticotropin.

SUMMARY

The activity of the adrenal cortex of twenty-nine male children up to the age of 11 years was studied by injecting corticotropin intramuscularly and determining the urinary excretion of 17-hydroxycorticoids and 17-ketosteroids. Urinary sodium and potassium determinations were also obtained.

Twenty-four of the twenty-nine children showed a positive response to corticotropin, as indicated by at least a 50 per cent increase in either the urinary 17-hydroxycorticoids or 17-ketosteroids. The five children who revealed no adrenocortical response were all under 3 months of age. The hormonal response to corticotropin was much greater in children over 10 months than under 10 months of age.

No consistent results were obtained with respect to urinary sodium and potassium excretions after the administration of corticotropin.

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A Measure of Prematurity

Issachar Loomis, born in Torrington, Connecticut, May 28, 1736. "He was so small at birth that he could be put in a tankard (3 quarts) and the lid closed, and he grew to be a man weighing over 200 lbs."

A STUDY OF VENOUS PRESSURE IN THE NEWBORN INFANT

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A STUDY of the literature fails to reveal any report of venous pressure measurements in the normal newborn infant within the first few minutes of life. Because such data would prove interesting and useful, the present study was undertaken.

Numerous technical difficulties were encountered early in the study. An attempt was made initially to measure the pressure in the veins of the hand, internal jugular vein, and antecubital space, but difficulty in introducing the needle into these sites made them unsatisfactory. The umbilical vein was then considered because of its accessibility, but the validity of the readings was questioned because of functional closure of this channel. It is believed, however, that this channel remains patent for three days postnatally and that as long as a positive pressure can be recorded in the veins, it is a true reflection of the pressure in the right side of the heart.[1]

METHOD

Instruments.—Both the Burch-Winsor phlebomanometer[2] and the Mortiz-Tabora manometer were used in this study. The phlebomanometer is an extremely sensitive instrument for measurement of venous pressure. A rubber tube leading to a glass adapter, which holds the hypodermic needle, also communicates with a small pressure chamber in which the pressure can be varied by turning a screw. When the pressure in the chamber is reduced, a small amount of aqueous solution of sodium citrate is drawn up into the needle to form a meniscus in a glass adapter. With insertion of the needle into the vein, the pressure causes blood to enter the needle and move the meniscus farther along the glass adapter. The pressure in the chamber is increased until the meniscus assumes the original position; the venous pressure is then registered on the column of water.[2]

Procedure.—Measurements with the phlebomanometer were made in the delivery rooms of the Charity Hospitals at New Orleans and Independence, Louisiana, during the months of January and February, 1955. After the infant was delivered, the cord was clamped and cut, the infant was placed on his back on the table to eliminate gravitational effects, and the needle was inserted into the umbilical vein at a distance of 10 cm. from the umbilicus. Correction for position was made by adjusting the site vertically to the level of the right auricle, and the venous pressure was then recorded.

This work was done in fulfillment of the requirement for a Senior Thesis by the Department of Medicine, Tulane University School of Medicine, New Orleans, La.

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An attempt was made to measure the venous pressure within the first few seconds of life, when the infant was not cold, crying, or kicking, since these factors obviously increase venous pressure significantly. Sixteen of the seventeen measurements in this series were recorded within the first sixty to two hundred forty seconds after delivery; the last was made by passing a polyethylene tube into the umbilical vein of an infant in the fifth hour of life.

was passed with ease at a distance of 6.5 cm. from the umbilicus, the right side of the heart being used as a base, and the height of the column of blood was measured at 80 mm. H_2O. It was noted during the study that when the obstetrician stripped the vein, the pressure was increased over the average for the series. No undesirable effects were observed in any of the infants studied in these experiments.

When the infant was still and no other disturbances existed, the phle-

TABLE I. VENOUS PRESSURE IN UMBILICAL VEIN OF NORMAL NEWBORN INFANT

CASE NO.	VENOUS PRESSURE (MM. H_2O)	INTERVAL FROM CLAMPING OF CORD (SEC.)	DISTURBANCES DURING MEASUREMENT
1	80	60	
2	80	60	
3	80	60	
4	85	60	
5	85	60	
6	85	60	
7	88	60	
8	94	60	
9	80	60-90	
10	80	60-120	
11	90	60-120	
12	140	90-120	Infant crying
13	180	90-120	Cord stripped
14	80	120-180	
15	120	120-180	?
16	98	180-240	
17	80	18,000	
Mean of 14 measurements taken under standard conditions	85		

RESULTS

Results are summarized in Table I. In this series of seventeen determinations, venous pressure varied from 80 to 180 mm. H_2O. The measurements obtained on warm, still infants, with no disturbances, varied from 80 to 98 mm. H_2O (mean 85 mm. H_2O).* In the last measurement, obtained at 5 hours of life, the polyethylene tube bomanometer was by far the more suitable instrument for this purpose. In the presence of such disturbing factors and consequent fluctuation in the readings, however, the Mortiz-Tabora manometer proved more satisfactory. The phlebomanometer offered the advantage of convenience and facility of manipulation, whereas the Mortiz-Tabora manometer necessitated sterilization of the instrument for each determination.

Factors that may have influenced these measurements include the use

*Using this technique, Dr. A. R. Singleton, of the Independent Obstetrics Service, Charity Hospital, New Orleans, obtained one measurement of 86 mm. H_2O under standard conditions in an infant not included in this series.

of drugs, such as vasopressor agents. These were not studied in the present series but should be investigated.

SUMMARY AND CONCLUSIONS

A study of the venous pressure in the newborn infant was carried out within the first few minutes of life. Determinations were made in the umbilical vein at a distance of about 10 cm. from the umbilicus with the infant in the reclining position, the site being adjusted to the level of the right side of the heart. The mean venous pressure for fourteen determinations obtained under standard conditions was 85 mm. H_2O.

It seems important that determinations be made (1) within the first few minutes of life, before functional closure of the channel occurs and (2) when conditions are standard, i.e., when the infant is not cold, crying, or contracting. On two occasions it was noted that stripping the cord increased the readings significantly. No untoward effects from this procedure were noted in this study.

I wish to acknowledge the valuable guidance and assistance of Dr. G. E. Burch in the conduct of these experiments.

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About the year 1785, the Scarlet-Fever, with sore-throat, appeared among the children at Detroit, and swept off, in this little place, upwards of sixty children, and even a few grown persons, in the term of a few weeks. Our Indian congregation, then living in the neighbourhood, though they frequently visited this place, never took the disorder. A person at Detroit then remarked to me, that this disease did not affect the children of French-Canadians as much as it did those of Europeans. However, a disorder called the Hooping-Cough, attended, at length, with a sore-throat, I have known to prove destructive to the Indian children, in their settlements.

—PHILADELPHIA MEDICAL & PHYSICAL JOURNAL, 1804.

RELATIONSHIP BETWEEN CLINICAL STATUS AND BEHAVIOR TEST PERFORMANCE IN A NEWBORN GROUP WITH HISTORIES SUGGESTING ANOXIA

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IN PREVIOUS papers,[1, 2] the development and standardization of several test procedures designed to assess the behavioral status of newborn infants have been reported. The performance of traumatized infants, including anoxic, birth-injured, erythroblastotic, and other groups, was discriminably different on these behavioral tests from that of normal controls. In the present paper, the ability of the tests to discriminate among a more homogeneous group of infants is considered. The group studied consists of sixty "anoxic" infants, some with observable postnatal anoxia and some with possible prenatal anoxia. While all of these infants may have experienced a period of anoxia, they varied considerably in their postnatal clinical condition and, accordingly, in the degree to which they aroused concern in those caring for them. Our purpose was to determine whether differences in the seriousness of the clinical condition would be reflected in differences in test performance. In order to do this it was necessary to develop a quantitative method of estimating clinical condition. In this paper we shall describe the Behavior Test procedures and the methods developed for measuring clinical condition. Then data will be presented on the way these variables relate to one another.

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METHODS

Subjects.—The subjects were sixty full-term infants born on the inpatient service of the St. Louis Maternity Hospital during the period from July, 1953, through October, 1955. They include forty-six infants apneic at birth or postnatally, but without other serious illness or evidence of mechanical birth injury. This group was composed of almost the total population of such infants born during this period. In addition there were fourteen infants without signs of extrauterine anoxia whose history included either maternal complications during pregnancy, a long and difficult labor, or signs of fetal distress during labor. The fourteen subjects were all the cases having these signs, from a group of 128 unselected infants on whom we had made both blood oxygen and behavioral studies. Finally, twelve additional infants used for the pediatric ratings were examined before the Behavior Test battery was completed and were

therefore not available for the analysis relating clinical condition to Behavior Test performance.

Behavior Tests.—The test procedures consist of a pain threshold test, a maturation scale, a vision scale, an irritability rating, and a muscle tension rating. The total battery takes from thirty minutes to an hour to administer and is not disturbing to the infant.

Detailed instructions and methods of standardizing the procedures have been reported in earlier papers,[1, 2] and only a brief description of the procedures is necessary here.

(1) *Pain Threshold Test:* Impairment of sensory functioning has proved a useful sign of brain damage in the adult. With neonates the number of sensory modalities which can be studied is limited because of the difficulty of determining when a discrete response to the stimulus has occurred. However, it is fairly easy to detect specific responses to mild electrical stimuli. These are administered to a small area just below each knee

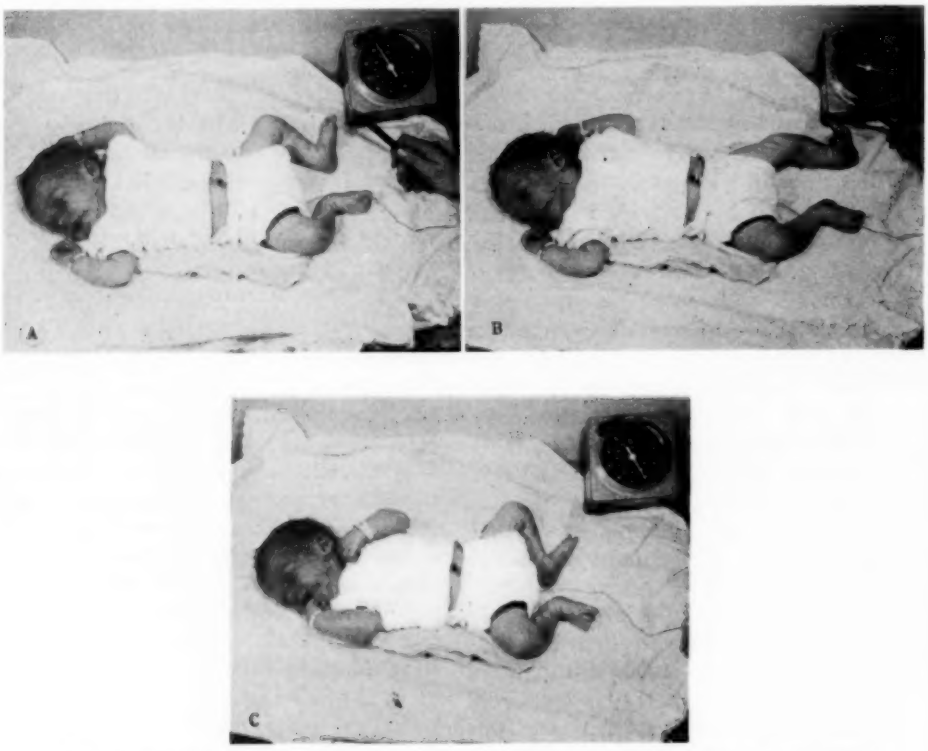

Fig. 1.—These pictures demonstrate a typical response sequence to the pain threshold procedure. In *A*, the baby, a 1-day-old full-term male, is lying quiescent on the mattress. *B* was taken immediately after a stimulus of medium intensity was applied to a spot just below the left knee. The response is a clear, discrete extension of the leg with some flexion of the foot. In *C*, taken 5 seconds after removal of the stimulus, the baby is again in a relaxed position with both legs flexed.

by means of an electronic stimulator designed by Bishop.[3] Four series of stimuli of varying intensity are applied until the threshold in volts just sufficient to elicit movement of the stimulated limb is determined. A photographic illustration of a typical response sequence is shown in Fig. 1.

tion, response to mildly annoying stimuli such as a small piece of cotton or paper placed above the upper lip or over the nose, strength of grasp, and vigor and persistence of response to several of the items. A response is scored in terms of its maturity as determined by the modal reactions of

Fig. 2.—These pictures illustrate contrasting responses of a premature and a full-term baby to two of the items on the maturation scale. *A* and *B* demonstrate the babies' responses to being placed prone. The premature baby barely turns his head to clear the mattress and earns a score of 1 point. The full-term baby is shown lifting his head to clear the mattress, a response which earns a score of 2. *C* and *D* show contrasting responses to the ringing of a bicycle bell. The premature baby gives a relatively undifferentiated Moro response. The full-term baby turns his head toward the stimulus and diminishes motor activity as though listening.

(2) *Maturation Scale:* The examiner observes the infant's behavior under a variety of stimulating conditions, such as head and leg reactions when placed in the prone position, leg response to pressure, auditory reac-

infants tested on each of the first five days of life. In general, responses which are relatively specific and stimulus-oriented are more mature and receive greater credit, as illustrated in Fig. 2. Total score on this scale may

range from 0 to 21. Many of these items have been adapted from Gesell and Armatruda[4] and from infant tests designed for older children.

(3) *Vision Scale:* Gesell and coworkers[5] have pointed out that visual responses of fixation and pursuit may be seen in the newborn infant when opportunities for observation are favorable. By standardizing the methods of examination and the criteria used in scoring, it was possible to determine a rough continuum of visual response. Scoring takes into consideration the presence or absence of certain responses (such as uncoordinated eye movements, fixation, or pursuit), the ease of elicitation, and the direction and the distance through which the eye moves in pursuit of a stimulus. Scores from 0 to 10 are possible.

(4) *Irritability Rating:* On the basis of observations made during administration of the three previously described scales, a rating is made of the irritability shown by the infant. By irritability is meant the sensitivity of the infant to stimulation. Ratings are made on a three-point scale, the points being anchored by descriptions of behavior that include such factors as the kind and intensity of stimuli which evoke crying, the general state of the infant, the tone of the cry, and the ease with which the child can be quieted.

(5) *Muscle Tension Rating:* The purpose of this rating is to quantify deviations of muscle tone in the direction of either increased flaccidity or rigidity. As with the irritability rating, objectivity was increased by providing specific descriptions of behavior that should characterize a given numerical rating. Rating is based upon observation of the amount of spontaneous movement, the position of the limbs when the infant is in a relaxed state, the frequency of trembling of body parts, and the response to such procedures as limb displacement and being pulled from a supine to a sitting position. See Fig. 3 for illustration of this procedure.

All the tests show satisfactory reliability, and norms have been provided for each of the first five days of life and for Negro and white subjects, where these variables are related to performance. Private-clinic status and sex of the infant do not measurably affect performance.[2]

For this study subjects were examined, if possible, within twenty-four hours after birth, or as soon as the condition of the infant permitted. All subjects were given at least three of the five tests and the *average standard score* of tests given has been used as the single over-all measure of test performance. This is referred to as the *Behavior Test score.* By using standard scores, performances of different groups, as Negroes and whites, can be directly compared, since the scores of each group are converted to a standard distribution having a mean of 50 and a standard deviation of 10. The conversion values were determined by the performance of 265 normal subjects used in standardizing the tests.[2] Although the averages were in some cases based on three tests and in some cases on four and five tests, we were justified in treating the data as a whole as there was homogeneity of means and variances.

Clinical Prognostic Rating.—At present, the only method of evaluating all the factors converging on a single case, in order to arrive at a

prognosis, is to depend upon the acumen of the experienced clinician. Such clinical judgments have limited usefulness in research, unless they can be quantified—and even with quantification, they are dependent upon the consistency and skill of the individual judge. We have attempted, therefore, to devise an objective and routine method of assigning numerical weights to events reported in the medical chart.

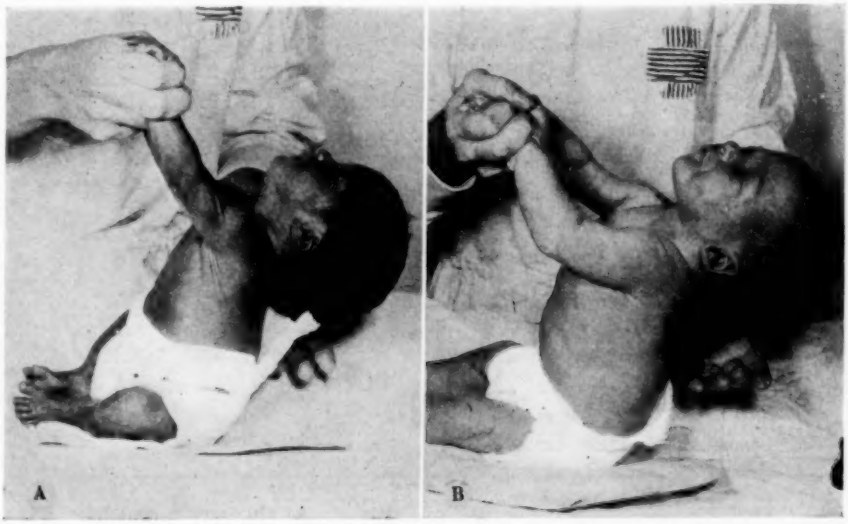

Fig. 3.—*A* and *B* illustrate responses of a full-term and a premature baby to one of the postural responses contributing to the rating of muscle tension. The premature baby, when pulled from a supine to a sitting position, shows marked head lag and completely relaxed shoulders. The full-term baby shows the increase in muscle tone which should accompany such a postural readjustment. Head lag, although present, is not marked.

This weighting method gives a prognostic score which agrees well with clinical judgments.

The weighting method used considered separately three categories of information available about an infant. The three categories were: (a) signs of fetal anoxia, (b) signs of anoxia at birth or subsequently, and (c) postnatal signs of central nervous system injury. A numerical rating from 0 to 3 was assigned each category on the basis of the number and kind of signs present and the weights were then combined into an over-all score. Detailed explanation is given below. Pediatricians will undoubtedly vary in their opinions of the relative importance of the various signs, but it should be remembered that the aim was to provide an over-all prognostic score which would compress with reasonable accuracy the complex of variables to be found in a neonatal history.

All the data from which the ratings have been made are provided in the medical chart. Medical histories suffer from an unknown degree of unreliability, and it would certainly be preferable had the material been gathered specifically for research purposes. In spite of its research limitations, however, the medical chart is a

valuable source of information which can presumably be made more valuable by quantifying the data it contains. It should be added that the records used in this study include a specially prepared summary sheet on which information about prenatal and perinatal factors can be conveniently checked. This has been in routine use in this center for a number of years and tends to reduce errors of omission that are likely to be present in descriptive notes.

Table I, Part A, lists the weights assigned to various signs in the first category of fetal anoxia. These were totaled for each infant and then converted into a rating having a maximum of 3, by means of the tabulation in Part B. It will be noticed that difficulties during labor are included in this category, since it is possible that anoxia prior to delivery may not be fully reflected by the condition of the infant at birth. The aim of the weights and of the final rating is to reflect the likelihood that an infant's prenatal experience has led to a period of anoxia. They have been assigned with the idea that certain conditions are much more serious than others, but that the presence of several signs, less significant if considered alone, increases the probability of anoxia. It should be added that we have attempted to rate only those conditions which have occurred in the approximately 350 infants studied

TABLE I. WEIGHTS ASSIGNED TO VARIOUS SIGNS OF FETAL ANOXIA

PART A

0.5	1.0	2.0	3.0
Maternal conditions: pre-eclampsia, diabetes, severe anemia	Maternal conditions: severe pre-eclampsia, uncontrolled diabetes, moderate renal insufficiency	Maternal conditions: eclampsia, diabetic coma, advanced renal insufficiency, decompensated heart disease	Maternal conditions: prolonged eclampsia
Bad reproductive history			
Notably infarcted placenta	Postmature syndrome		
Marginal placenta previa or other third trimester bleeding		Central placenta previa or partial abruptio placenta	Complete abruptio placenta
Amnionitis; endometritis	Polyhydramnios	Severe polyhydramnios	
Cord tight or coiled several times	Prolapsed cord		
Uterine inertia, prolonged labor without progress, abnormally rapid or forceful labor	Membranes ruptured over 24 hr. Abnormal fetal heart rate		
Fever or acetonuria during labor	Meconium (not breech)	Meconium-stained infant	

PART B

TOTAL INDIVIDUAL WEIGHTS	RATING
0.5	0.5
1.0 to 1.5	1.0
2.0 to 2.5	2.0
3.0	2.5
3.5 and higher	3.0

as part of the total research project. No effort has been made to compile a comprehensive list of possible fetal complications associated with anoxia.

Table II lists the weights assigned to various signs in the second category, postnatal anoxia. The two factors considered in establishing the weights were the condition of the infant immediately after birth and the kind of resuscitation used. The infant's condition was judged primarily by the number of minutes of respiratory delay, the weighting having been empirically determined on the basis of other information recorded about the infant's condition, as inserted in parentheses in the table.

TABLE II. WEIGHTS ASSIGNED TO VARIOUS SIGNS OF ANOXIA AT BIRTH OR AFTER.

(Weights assigned to Parts 1 and 2 are averaged for birth anoxia. Only Part 1 is used in the case of anoxia after birth.)

PART 1	
WEIGHT	INFANTS' CONDITION
0.5	Sleepy, cyanotic, or cry delayed or absent
1.0	1-3 min. respiratory delay (cyanotic)
2.0	4-5 min. respiratory delay (hypotonic, cyanotic)
3.0	More than 5 min. respiratory delay (flaccid, pallid, gasping)

PART 2	
WEIGHT	RESUSCITATION EMPLOYED
0.5	Rubbing or oil
1.0	From 1 to 2 of the following: (with or without rubbing and oil) dilatation rectal sphincter, chemical stimulant, artificial respiration, O_2 per mask, resuscitator
2.0	More than 2 of the mild (1.0) resuscitation methods or tracheal catheter for aspiration* or Air Lock cycled *not* more than 30 min.
3.0	Tracheal catheter for insufflation or Air Lock cycled more than 30 min.

*Not scored for infants delivered by cesarean section.

Thus, when the respiratory delay of a newborn infant was recorded as from one to three minutes, the child was usually also checked as cyanotic. With longer delays, he would be described as hypotonic or flaccid. Whether the exact number of minutes was recorded accurately may be questioned, but the intervals chosen, at least on this particular obstetrical service, were associated consistently with the parenthetical description of the infant's general condition. A further check on the reliability of the measure of apnea was provided by taking into account the methods of resuscitation. These were weighted separately in terms of the practice in most general use on the obstetrical service. The weights assigned for respiratory delay and for resuscitation method were then averaged. Usually there was no disagreement between the two, and the rating for the category was the same as would be arrived at by considering only respiratory delay. Where there was disagreement, the averaging method provided a compromise solution. Recurrent anoxia after birth, as from hyaline membrane, was rated only in terms of the duration of the longest single period of apnea. If anoxia occurred both at birth and during the neonatal period, the scores were added, but the total could not exceed 3.0.

The third category, postnatal signs of central nervous system damage, was weighted in the manner shown in Table III. Weight was given both for the kind of sign and to the length of time that any CNS sign persisted. The weights for duration and seriousness of signs were then averaged to obtain a final rating for this category.

RESULTS

Agreement Between Pediatric Judgments and Weighted Prognostic Scores.—The prognostic score for each infant is the sum of the three subratings. To determine whether these scores actually agreed with clinical evaluations, the prognostic scores of a sample of thirty anoxic patients were compared with the clinical judgments which two pediatricians made from the neonatal records of these same cases. Originally, the two pediatricians, both experienced in the neonatal field, were asked to rank twenty-five infants, eighteen of whom were anoxic and seven of whom had suffered various other kinds of trauma, into as many discriminable groups as possible in terms of the seriousness of the clinical condition.[2] They found it difficult to make consistent judgments when trying to discriminate more that three degrees of seriousness. These three ranks were roughly identified as mild, moderate, and severe trauma—or good, questionable, and guarded prognosis. The latter description probably reflects more accurately the kind of judgment made, that is, an evaluation of the total clinical picture. This must necessarily consider future status as well as present condition. A second group of twelve infants, all of whom were anoxic, was subsequently classified in the same way, making a total of thirty anoxic infants whom the two pediatricians had independently classified as having good, questionable, or guarded prognoses.

The classifications showed high agreement with the weighted prognostic scores assigned to these infants. The eta correlations, determined from analyses of variance, were 0.92 between pediatrician A's classifications and the prognostic scores and 0.74 between pediatrician B's classification and the prognostic scores.* Pediatrician A had been consulted in setting up the weighting system and,

TABLE III. WEIGHTS ASSIGNED TO VARIOUS SIGNS OF CNS DAMAGE
(Weights assigned to Parts 1 and 2 are averaged to give the final rating.)

PART 1: SIGNS			
WEIGHT:	1	2	3
	One to three of the following mild signs:	More than three mild signs, or:	One or more of the following:
	Abnormally alert Somnolent Irritable Poor feeding Weak or high cry Increased or decreased tone Head retracted (not breech) Sleeps eyes open Weak sucking Abnormal Moro Jumping-jack reflex Lightly xanthochromic spinal fluid	Twitching and spasms Tense fontanel Nystagmus Abnormal pupils Cry absent Spinal fluid definitely xanthochromic or blood-tinged	Convulsions Sucking Absent Moro absent Spinal fluid grossly bloody

PART 2: DURATION OF ANY SIGN				
WEIGHT:	0	1	2	3
DURATION:	0-6 hr.	6-24 hr.	1-2 days	More than 2 days

*Correlation is a convenient statistic for measuring the degree of relationship, a perfect relationship being indicated by a correlation coefficient of 1.0 and only chance relationship by a coefficient of 0. In order to treat the data statistically, the pediatric classifications of good, questionable, and guarded were assigned arbitrary weights of 1, 2, and 3, respectively.

while she did not know the scores assigned to infants whom she rated, it is to be expected that she would agree well with the scores as long as she maintained consistent criteria.

The two pediatricians did not agree as well with one another as they did with the prognostic score. The eta correlation between their classifications was 0.63. While each assigned the same prognosis to nineteen of the cases, they disagreed on the remaining eleven. These disagreements were consistent in direction, however, and were due to the tendency of pediatrician A to rate the prognosis as relatively poorer. Table IV shows the mean prognostic scores of the thirty cases. The scores are higher where the prognosis was considered to be poorer. The eleven cases on which there was disagreement appear to be borderline cases. Their prognostic scores lie between the prognostic scores of cases with similar ratings on which both pediatricians agreed.

TABLE IV. MEAN PROGNOSTIC SCORES OF THIRTY CASES RATED BY TWO PEDIATRICIANS AS HAVING GOOD, QUESTIONABLE, OR GUARDED PROGNOSES

PEDIATRICIAN'S RATING	NO.	MEAN PROGNOSTIC SCORE
Ped. A—Good Ped. B—Good	13	1.1
Ped. A—Questionable Ped. B—Good	5	2.2
Ped. A—Questionable Ped. B—Questionable	3	2.8
Ped. A—Guarded Ped. B—Good	3	4.0
Ped. A—Guarded Ped. B—Questionable	3	5.4
Ped. A—Guarded Ped. B—Guarded	3	5.5
Total	30	

Agreement Between Clinical Prognosis and Behavior Test Performance.—The findings show that a newborn infant's performance on behavioral tests is related to the over-all clinical prognosis. Using the ratings of the two experienced pediatricians as the measure of clinical prognosis, we find that those infants with guarded prognosis gave a much-impaired performance as compared with those for whom the prognosis was questionable or good. Table V shows the ratings given and the Behavior Test scores for eighteen of the thirty infants who were rated. The remaining twelve were examined before the test battery was complete and data on their Behavior Test scores are not available.

A more sensitive estimate of the relationship between behavior and clinical status can be obtained by using the weighted prognostic scores as the measure of clinical prognosis. Fig. 4 provides a pictorial illustration of the relationship. The mean Behavior Test scores are plotted against the prognostic scores. All sixty anoxic infants are included, the number contributing to the mean score at each point being shown in the legend. For purposes of comparison, the scores of sixty-two normal subjects are also included on the graph. These are unselected subjects with no complications recorded in the medical history, whose prognostic scores are, therefore, 0. It will be noticed that there is no reversal in the downward trend of the curve.

Points on the graph represent the mean of the Behavior Test scores obtained by groups of subjects. All subjects whose prognostic scores fell in the same interval did not, of

course, give the same performance on the behavior tests. Fig. 5 shows the range of Behavior Test scores within each of the groupings. The distribution of these scores in the normal control group approximates the familiar normal probability curve and the variability is relatively small. None of the normal subjects obtained a score less than 35, which is one and one-half standard deviations below the mean. This is not true of the distribution of scores in the anoxic groups. The range of scores is wider and the curve is flattened. Except for the group with the lowest prognostic scores, i. e., for those most like the control group, there is little tendency for the scores to cluster at any one point.

The Behavior Test score, or average standard score, was the measure of an infant's over-all performance on the battery of five tests. Scores on

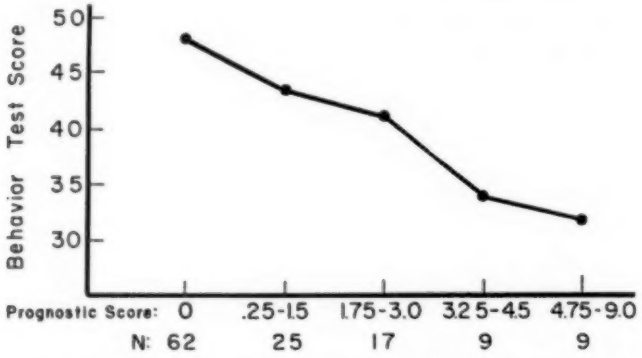

Fig. 4.—Relationship between an estimate of clinical prognosis and behavioral test performance of sixty-two normal and sixty anoxic newborn infants.

TABLE V. BEHAVIOR TEST SCORES OF EIGHTEEN ANOXIC INFANTS RATED AS HAVING GOOD, QUESTIONABLE, OR GUARDED PROGNOSES

CASE	PROGNOSTIC RATING BY		BEHAVIOR TEST SCORE	MEAN BEHAVIOR TEST SCORE OF INFANTS WITH SAME RATINGS
	PEDIATRICIAN A	PEDIATRICIAN B		
1	Good	Good	52	
2	Good	Good	52	53.7
3	Good	Good	57	
4	Questionable	Good	25	
5	Questionable	Good	32	36.7
6	Questionable	Good	53	
7	Questionable	Questionable	26	
8	Questionable	Questionable	40	39.0
9	Questionable	Questionable	51	
10	Guarded	Good	8	
11	Guarded	Good	48	36.3
12	Guarded	Good	53	
13	Guarded	Questionable	22	
14	Guarded	Questionable	32	29.7
15	Guarded	Questionable	35	
16	Guarded	Guarded	18	
17	Guarded	Guarded	22	26.0
18	Guarded	Guarded	38	

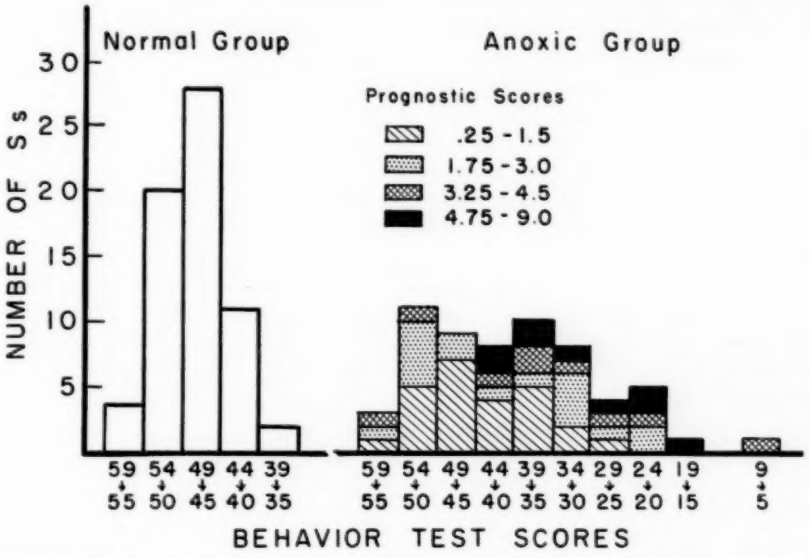

Fig. 5.—Distribution of behavior test scores of sixty-two normal and sixty anoxic newborn infants.

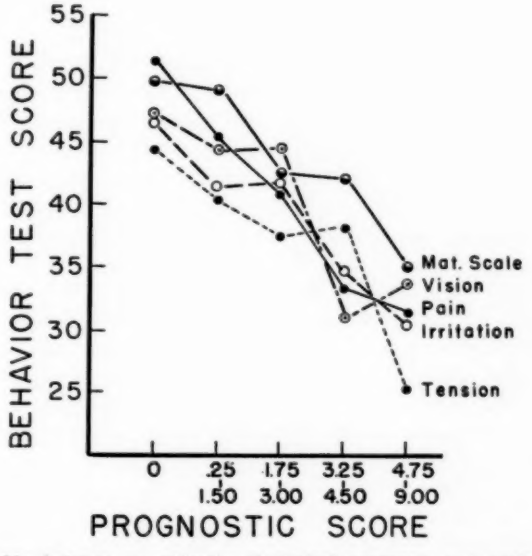

Fig. 6.—Relationship between an estimate of clinical prognosis and performance on each of five behavioral measures in sixty-two normal and sixty anoxic newborn infants.

each of the five tests are plotted separately in Fig. 6. Impaired performance occurs on all of the tests as the prognosis becomes poorer, but the relationship is not as regular as when the more reliable Behavior Test score is used.

The above results give evidence of a relationship between clinical prognosis and behavioral test performance. The degree of this relationship can be estimated more accurately by the Pearson correlation coefficient.* This correlation was 0.46 for the relationship between the Behavior Test score and the prognostic score of the sixty anoxic infants. When the sixty-two normal infants with prognostic scores of 0 are also considered, thus increasing the heterogeneity of the group, the correlation rises to 0.59.

DISCUSSION

The neonatal period is generally regarded as crucial for later development. Quite literally it is a "life-or-death" period, and the infant who survives the first week of life earns for himself a much more secure position on the actuarial table. Yet despite the importance of this time as a significant developmental period in itself, there is a tendency to regard it only as transitional and to use later periods for judging the effects of certain experiences, such as birth injury or anoxia, occurring during the first few hours and days of life. This is indeed justifiable, as we are more concerned with lasting than with transitory effects. However, it is reasonable to suggest that immediate response will provide a better basis for predicting residual effects of an event than will information limited to the event itself.

Aside from concern with prediction of future status, it is important to be able to assay current developmental status during the neonatal period. For example, it is important to know something about the effects of certain obstetrical and anesthetic practices on the immediate status of the infant as well as on his status some years in the future, by which time many variables will have confounded the relationship. Thus we were interested in developing procedures which would be reliable and sensitive indicators of an infant's behavioral status during the first five days of life.

The "Behavior Tests for the Newborn" are standardized procedures, and differences in performance on them can be expressed in quantitative form. In order to determine whether the behavioral differences measured by these tests were relevant to clinical problems, two approaches have been used. In an earlier paper,[2] the performances of traumatized and normal groups were compared. Infants with uncomplicated prenatal and perinatal histories were found to perform significantly better than those with complications. In the present paper, we attempt to show that not only did groups differ but also that within a group of infants, with varying but unknown amounts of anoxia, the degree of impairment in test performance reflected the seriousness of the clinical condition.

This was true whether seriousness of clinical condition was determined by the ratings of two experienced pediatricians or by the method of weighting multiple factors in the neonatal history. The weighting method seems preferable, since it not

*Pearson correlations can be used when there is reason to think that the relationship between two variables is linear. The coefficient is interpreted in the same way as the eta correlation. See preceding footnote.

only assures consistent criteria and agreement among different raters using the method but because it also allows finer differentiation among infants. The two judges did not feel that they could satisfactorily distinguish more than the three categories of good, questionable, and guarded prognosis.

The Behavior Tests thus provide a method of assessing the behavioral status of the newborn infant—a method which is sensitive to small differences in the past history of the organism. Such a method should prove useful in evaluating the effects of particular kinds of experiences, such as obstetrical complications, diseases of pregnancy, etc. By employing an evaluating criterion which detects degrees of minor impairment, it is possible to carry out research with smaller numbers of subjects than is acceptable if one must depend upon such a gross criterion as mortality rates in large groups. It is hoped that the method may also prove valuable in detecting at this early age the child who will show later developmental defects. In this connection, it is of interest that the range of Behavior Test scores was greater in the anoxic group than in the controls. Some infants who were subjected to anoxia and whose prognosis seemed uncertain did not show any impairment on the Behavior Tests, while others with a similar history were markedly impaired. It is reasonable to predict that the casualties in later development will be found in the latter group. In order to test this prediction, as many as possible of both the anoxic and the normal infants are being followed and reexamined at later periods of life.

SUMMARY

A battery of five behavioral tests designed and standardized for newborn infants was administered to a group of sixty "anoxic" infants, including those with observable postnatal anoxia and those with possible prenatal anoxia, and to a group of sixty-two normal infants. The five tests consisted of a pain threshold test, a maturation scale, a vision scale, an irritability rating, and a muscle tension rating. The degree of impairment in test performance reflected the seriousness of the clinical condition, both when the clinical history was evaluated by two experienced pediatricians and when it was estimated by a method of weighting multiple factors in the medical history. The behavioral tests thus appear to provide an objective, quantitative, and sensitive method of assessing the clinical status of a newborn infant.

We are indebted to the authorities of the St. Louis Maternity Hospital and to the obstetricians and pediatricians who provided the opportunity for carrying out the study. We should like to express special gratitude for the cooperation of the nursing staff and especially of Margaret Weber.

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EVALUATION OF SULFAETHYLTHIADIAZOLE (SETD) IN COMMON INFECTIOUS STATES IN CHILDREN

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PROLONGED or repeated exposure to antibiotics is known to induce the development of antibiotic-resistant organisms, superimposed fungal infections, and sensitization reactions. Several precautionary methods have been suggested to overcome these complications of antibiotic therapy.[1-3] One of the more practical methods, the use of less potent drugs in treating common infections, has been partly responsible for a renewed interest in the use of sulfonamides. According to Yow,[4] a more widespread use of sulfonamides may delay the formation of antibiotic-resistant organisms and may thereby enhance the efficacy of antibiotics when they are used to treat serious illnesses.

The purpose of this report is to present clinical and laboratory data obtained in treating 512 pediatric patients with a newly available sulfonamide, sulfaethylthiadiazole* (SETD). Although SETD has had extensive use in Europe,[5-8] its pharmacological and bacteriological properties have been re-evaluated by American investigators. Foltz and associates[9] report that SETD is rapidly absorbed from the gastrointestinal tract, producing in adults blood levels between 14 and 20 mg. per cent within two hours after the administration of a 4.0 Gm. oral dose. They also found that 75 to 80 per cent of the drug could be recovered from the urine in twenty-four hours, and that virtually complete urinary recovery occurred within seventy-two hours. Since the acetylation of SETD in the body is low (1 to 5 per cent in blood and 5 to 10 per cent in urine), over 90 per cent of the drug is available for antibacterial activity.[10] Results of solubility tests indicate that SETD is readily soluble in human urine over the usual pH range. Rhodes[11] reports that the antibacterial spectrum of SETD covers most of the gram-positive and gram-negative pathogenic organisms.

From the Lankenau Hospital.

*N1-(5-ethyl-1,3-4-thiadiazol-2-yl)-sulfanilamide.

MATERIAL

Three pharmaceutical forms of SETD were used to treat patients during the study: a tablet, a liquid, and a sustained-release suspension. The latter preparation* consisted of thousands of micropellets containing SETD suspended in a fruit-flavored vehicle. The micropellets were designed to disintegrate at varying rates to produce promptly therapeutic blood concentrations of the drug that last about twelve hours. Each tablet and each teaspoonful of the liquid contained 500 mg. of SETD. Each teaspoonful of the sustained-release form contained 650 mg. of SETD.

*Supplied as Sul-Spansion by Smith, Kline & French Laboratories, Philadelphia, Pa.

METHODS

A group of 512 patients (253 boys, 259 girls) ranging in age from 2 months to 11 years were treated for bacterial infections seen in everyday pediatric practice. Of the 444 patients who received SETD alone, 298 received either the tablet or the liquid form and 146 received the sustained-release suspension. The remaining sixty-eight patients, chiefly those with advanced otitis media or exudative tonsillitis, were given a single injection of 300,000 units of aqueous procaine penicillin initially, in addition to SETD.

Patients were seen either in the office or at their homes. Diagnoses were based on physical examinations; blood counts and urinalyses were done on many patients as further diagnostic aids. Where feasible, bacterial cultures (throat, ears, urine, or skin) were made to identify the infecting organisms.

At the beginning of the study only the tablet and liquid forms of SETD were available. Usually, but not always, older patients received tablets while younger patients were given the liquid. Daily doses of either of these forms of SETD were based on the patient's weight, 1 grain (65 mg.) of the drug being administered per pound of body weight per day. To maintain drug blood concentrations within the optimal therapeutic range of 8 to 15 mg. per cent, the tablet and liquid dosage forms had to be given every six hours. As with other sulfonamides, rapid onset of antibacterial activity was obtained by making the initial dose double that of the maintenance dose.

Once the sustained-release suspension became available, the use of tablet and liquid dosage forms was discontinued. Since reports of other investigators[12] indicated that the sustained-release form produces higher blood concentrations than does either the tablet or the liquid, daily doses of the suspension were based on only ¾ grain (50 mg.) per pound per day. The suspension dosage form was given only twice daily because its sustained-release properties produce blood concentrations of the drug within therapeutic range for twelve hours.

Blood concentrations of SETD produced by the liquid form were measured in six patients; concentrations produced by the sustained-release suspension were measured in twelve patients. Blood specimens (0.2 ml.) were taken from the patients' fingers at 2, 6, 8, 14, 20, 26, 30, and 36 hours after the initial dose of the drug was given. Specimens were mixed with a saponin solution and refrigerated until analysis could be carried out. Free and total (free plus conjugated) concentrations of SETD were analyzed according to Frisk's[5] modification of the Marshall-Bratton technique.

RESULTS

Results of therapy obtained with the tablet and liquid dosage forms of SETD are shown in Table I and results with the sustained-release suspension in Table II. A "good" result was recorded if, after three days of treatment, body temperature was normal and if clinical manifestations of the infection were markedly lessened or had disappeared. All other results were graded "poor." The duration of treatment was four to five days in most cases. Since patients were followed closely in this

study, observations were made to determine whether extension or complications resulting from the original infection occurred.

"Good" results were achieved in 97 per cent of both groups. There was no significant difference in efficacy between the group receiving the tablets or liquid and the group receiving the sustained-release preparation. As indicated in Tables I and II, "good" results were seen in all types of infections treated. Of the 298 patients who received SETD in tablet or liquid form, fifteen patients developed mild diarrhea, one a mild rash, and one persistently vomited after receiving the drug. Only one of the 146 patients who were given the sustained-release suspension experienced a side effect, mild diarrhea. No signs of renal toxicity or sensitization reactions to SETD were observed.

TABLE I. RESULTS OF THERAPY WITH SETD AND SETD-PENICILLIN

DIAGNOSIS	NO. OF PATIENTS RECEIVING		RESULTS			
	TABLET OR LIQUID SETD	SETD PLUS PENICILLIN	SETD		SETD + PENICILLIN	
			GOOD	POOR	GOOD	POOR
Tonsillitis	16	8	14	2	8	0
Bronchitis	16	4	16	0	4	0
Otitis media	26	35	26	0	35	0
Nasopharyngitis	229	2	221	8	2	0
Pneumonia	2	0	2	0	0	0
Croup	3	0	3	0	0	0
Urethritis	3	0	3	0	0	0
Other	3	1	3	0	1	0
Total	298	50	288	10	50	0

TABLE II. RESULTS OF THERAPY WITH SUSTAINED-RELEASE SETD AND SUSTAINED-RELEASE SETD-PENICILLIN

DIAGNOSIS	NO. OF PATIENTS RECEIVING		RESULTS			
	SUSTAINED-RELEASE SETD	SETD PLUS PENICILLIN	SETD		SETD + PENICILLIN	
			GOOD	POOR	GOOD	POOR
Tonsillitis	17	5	17	0	5	0
Bronchitis	9	1	9	0	1	0
Otitis media	13	11	13	0	10	1
Nasopharyngitis	102	0	101	1	0	0
Pneumonia	1	1	1	0	1	0
Lymphadenitis	3	0	3	0	0	0
Impetigo	1	0	1	0	0	0
Total	146	18	145	1	17	1

TABLE III. COMPARISON OF RESPONSE TO SETD THERAPY AND BACTERIOLOGIC FINDINGS

ORGANISM	NUMBER OF TIMES ISOLATED	RESPONSE TO SETD THERAPY	
		GOOD	POOR
Hemolytic streptococcus alpha	24	24	0
Hemolytic streptococcus beta	19	19	0
Nonhemolytic streptococcus	45	45	0
Hemolytic *Staph. aureus*	21	21	0
Nonhemolytic *Staph. aureus*	18	18	0
Hemolytic *Staph. albus*	2	2	0
Pneumococcus	59	58	1
Esch. coli	7	7	0
Pseudomonas	3	2	1
Total	198	196	2

In Table III, the response of patients to SETD therapy is compared with the organisms found in their cultures. Pneumococci and nonhemolytic streptococci were found as the infecting agents most frequently; isolations of hemolytic *staphylococcus albus* and Pseudomonas were too infrequent to permit the evaluation of SETD against infections caused by these organisms. Of the nine different organisms isolated, none were found resistant to SETD.

Blood concentrations of SETD produced by the liquid and the sustained-release suspension are compared in Fig. 1. Free and total blood concentrations of SETD produced by the sustained-release suspension are shown in Fig. 2.

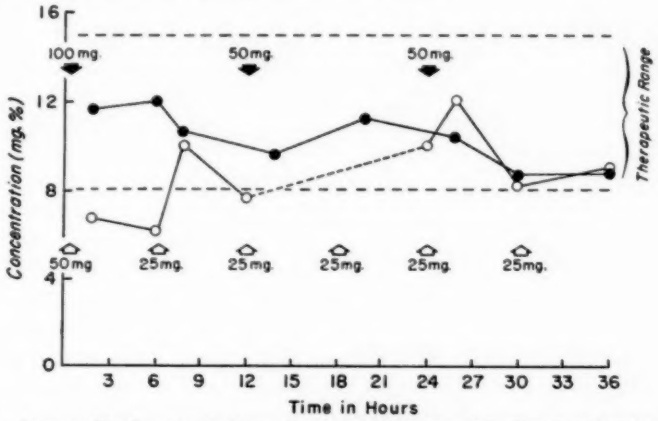

Fig. 1.—Average blood concentrations of free SETD produced by liquid and sustained-release dosage forms. Black arrow and black circle: sustained-release SETD (average of twelve patients). White arrow and white circle: liquid SETD (average of six patients).

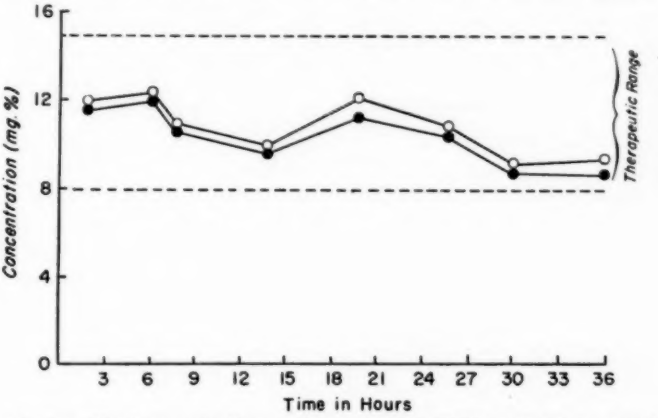

Fig. 2.—Average blood concentrations of free and total SETD produced by sustained-release dosage form. White circle: total SETD (average of twelve patients). Black circle: free SETD (average of twelve patients).

DISCUSSION

According to Hardy,[13] 15 to 20 per cent of patients who have simple upper respiratory tract infections develop complications (otitis media,

pneumonia, sinusitis, or bronchitis) as sequelae to the original infection. The lack of complications following SETD therapy may be related to the continuous therapeutic blood concentrations prevalent during the entire course of therapy.

The compatibility of combined therapy with SETD and antibiotics is emphasized by the excellent results obtained by a single injection of penicillin and a four- to five-day regimen of SETD in those patients with severe infections, particularly where a heavy, purulent exudate was present. Moreover, since experience has shown that a single injection of penicillin does not completely arrest infections of this type, SETD serves as a highly effective chemotherapeutic adjunct.

Its effectiveness against nine different organisms in this study gives some idea, although not a complete one, of the antibacterial spectrum of SETD. Rhodes[11] also found SETD to be effective against *Aerobacter aerogenes, Klebsiella pneumoniae, Hemophilus influenzae, Proteus vulgaris, Salmonella typhosa,* and others.

Determinations of blood concentrations, shown in Fig. 1, indicate that the sustained-release suspension produces drug concentrations consistently within the accepted therapeutic range of 8 to 15 mg. per cent. Since patients frequently fail to adhere to dosage regimens, the sustained-release suspension offers the advantage of continuous therapeutic blood concentrations for twelve hours following a single dose. Moreover, in children to whom the administration of medications is often difficult, less frequent administration of the sustained-release suspension is a great advantage.

Based on the determinations of free and total sulfonamide concentrations, only 2.2 per cent of SETD becomes acetylated in the blood (Fig. 2). Since the nonacetylated drug is the only form that possesses antibacterial activity, more than 95 per cent of the total dose of SETD is available for therapeutic purposes.

The low incidence of side effects produced by SETD, particularly the sustained-release suspension, indicates that the drug is well tolerated. The continuous release of small amounts of the active drug and its complete absorption from the gastrointestinal tract may account for the smaller number of side effects produced by the sustained-release suspension.

This study presents a method of management of patients in everyday practice which successfully shortens the course of infections, virtually eliminates bacterial complications, and produces a negligible incidence of side effects. The efficacy of penicillin, tetracycline, streptomycin, and chloramphenicol is not questioned. What is seriously questioned is the advisability of using these antibiotics in most of the respiratory and other infections seen in everyday practice. Such use or abuse leads to the development of resistant organisms and a high incidence of anaphylactoid and other side effects.

SUMMARY

1. Sulfaethylthiadiazole (SETD), a newly available sulfonamide, was used to treat 512 pediatric patients who had bacterial infections (chiefly of the respiratory and urinary tracts) commonly seen in everyday practice. SETD in tablet or liquid form was ad-

ministered to 298 patients; 146 were given the drug as a sustained-release suspension. An additional sixty-eight patients (with advanced infections) received an initial injection of procaine penicillin followed by SETD therapy.

2. Results of therapy indicate that SETD is a highly effective antibacterial agent. SETD shortened the course of infection and prevented any extension or complication of the original infection in about 97 per cent of the patients. A combination of SETD therapy and an initial injection of penicillin proved effective in advanced and severe infections.

3. Of the 298 patients treated with SETD in tablet or liquid form, fifteen developed mild diarrhea, one a mild rash, and one vomited. Mild diarrhea was observed in only one of the 146 patients who received the sustained-release suspension. None of the patients developed gross hematuria or other renal complications. Except for one skin rash, there was no other evidence of sensitization or toxicity related to the administration of SETD.

4. Therapeutic blood concentrations (8 to 15 mg. per cent) of SETD were obtained with the plain drug, provided the drug was given every six hours. A single dose of the sustained-release suspension produced therapeutic blood concentrations for twelve hours.

5. An average of only 2.2 per cent of SETD undergoes acetylation in the blood, indicating that more than 95 per cent of the total dose is available for antibacterial activity.

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ADDENDUM

Approximately 500 children with common infections have been treated with the sustained-release preparation since this report was submitted for publication. The results of therapy closely parallel those reported herein. This additional experience supports the findings that the sustained-release suspension of SETD is an effective and safe chemotherapeutic agent.

A CLINICAL APPROACH TO INFANTILE COLIC

A Review of Ninety Cases

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CONSIDERING its frequency in private practice, the subject of infantile colic has received little attention in recent medical literature. Anderson[1] defines "three-month" colic as a syndrome of abdominal pain manifested by a screaming infant with a suffused face, arms and legs drawn tightly against the trunk, the abdomen distended and rigid, but relaxing between the paroxysms of pain. Such attacks, occurring at regular daily intervals, with onset at about 3 weeks of age and continuing until some time during the third month of age, would be considered as a classical picture of "three-month" infantile colic, the duration and frequency of attacks determining the severity of the syndrome. In all instances an adequate history and thorough physical examination are necessary to rule out other conditions which may resemble this syndrome. The commonest of these are otitis media, gastroenteritis on an infectious basis, proctitis, anomalies of the gastrointestinal tract including persistent proctodeal membranes, and anomalies of the genitourinary tract.

The present study was undertaken in an attempt to evaluate the role played by hunger, feeding technique, diet, and other factors in the production of infantile colic.

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MATERIAL AND METHODS

The present study was carried out on infants seen in my private practice and at the University of Illinois Pediatric Outpatient Department, who showed the typical picture of colic described by Anderson.[1] Ninety infants were studied, six Negro and eighty-four white. Fifty of these infants were male, forty were female. There were two premature infants.

The following routine was carried out on all infants as soon as the diagnosis of infantile colic had been made:

1. The mother (and father, if necessary) was instructed in proper feeding technique. Emphasis was placed on the infant's proper grasp of the nipple, the proper size for the nipple orifices, avoidance of bottle holders, "burping," the length of time the usual feeding should take, the temperature of the milk, etc. In all cases the feeding of the infant was personally observed at least once, preferably in the home.

2. The feeding was increased in volume and frequently concentrated. In many cases solid foods were added.

3. The formula was changed by eliminating previously added carbohydrate.

4. The formula was again changed, reducing the content of butterfat by 50 per cent or more. In most instances a half-skimmed powdered milk was used (Alacta); in others, liquid skimmed milk and homogenized milk were mixed in the desired proportions.

5. In an attempt to determine whether the colic was due to milk allergy, a formula free of cow's milk was used, either goat's milk, soybean milk, or Nutramigen.

This routine was carried out step by step until either all had been completed or the symptoms of colic had disappeared during one of the procedures. Changes in formula were limited to one every four or more days. When the symptoms disappeared with the first step and did not recur, the infant was placed in the "feeding technique group"; and, similarly, those whose symptoms cleared up with the second step fell into the "hunger group." If the colic cleared with any of the last three steps, an attempt was made to reproduce the symptoms with the apparently responsible agent, i.e., carbohydrate, butterfat, or milk protein. Only when this could be done was the infant classified in a specific group.

It was necessary to consider four more groups to complete the clinical classification:

6. Those infants in whom the removal of added carbohydrate produced a marked improvement but did not completely eliminate the colic. This group was classified as "carbohydrate intolerance plus a second factor."

7. Those infants in whom the symptoms of colic had disappeared and could not be reproduced. These infants were placed in the "unclassified group."

8. Those infants in whom the colic could be reproduced by a miscellaneous group of factors, such as vitamins, orange juice, etc.

9. Those infants in whom the colic persisted despite all of the above modifications in their diet, and in whom psychosomatic factors appeared more important than in the remainder of the groups. It is generally agreed that psychosomatic factors enter into every infant's existence early in life and play an important role in every case of infantile colic. In this group, however, these factors apparently outweighed all other influences, and these infants were therefore placed in a "psychosomatic group."

Ninety infants were studied with this approach in mind. All exhibited clinical evidence of colic. Nineteen of these infants failed to respond to the outlined routine and fell into the psychosomatic group. These made up 21 per cent of the total number. Of the remaining seventy-one infants, all showed great improvement and could be classified in one of the various groups (Table I).

TABLE I. INFANTILE COLIC: A CLINICAL CLASSIFICATION

CLASSIFICATION	NUMBER OF CASES	PER CENT
1. Feeding technique	2	2.2
2. Hunger	10	11.2
3. Carbohydrate intolerance	20	22.2
4. Fat intolerance	10	11.2
5. Allergy	9	10.0
6. Carbohydrate intolerance plus a second factor	8	8.8
7. Unclassified	8	8.8
8. Miscellaneous	4	4.4
9. Psychosomatic	19	21.2
Total	90	100.0

Since the etiological approach to an infant with colic may require a considerable period of time before results can be expected, it seemed desirable to give immediate relief with small doses of barbiturates and atropine or atropine-like drugs. Phenobarbital was used in amounts varying up to $\frac{1}{8}$ grain before each feeding, with atropine in amounts varying up to $\frac{1}{1,000}$ grain. It was our practice to discontinue these drugs on the third or fourth day of a new formula

change, since only in this manner could one determine whether progress was being made.

RESULTS AND DISCUSSION

Poor feeding technique was a factor in only two of the ninety infants studied. In both of these cases the symptoms were severe and almost continuous, but completely disappeared when proper feeding methods were used. The number of cases of poor feeding technique would undoubtedly be greater in an unselected group. The small number (2.2 per cent) is probably due to the fact that in private practice proper feeding technique is stressed at the time of the first contact with the mother of a newborn infant.

The second group in our series involved those ten infants in whom the symptoms of colic were apparently due to hunger. This classification accounted for 11.2 per cent of the ninety cases, a much smaller percentage than one would expect from the reports in the pediatric texts.[1] The age of onset (2.2 weeks) in this group was lower than for the ninety cases in the entire group (2.9 weeks). The differential diagnosis between a hungry baby and one with a case of infantile colic due to hunger was made from the history. In the former, crying occurred either immediately after feedings or within a half hour, the infant was readily pacified with an additional feeding, and the other symptoms of colic were not present. In the infant with colic the crying occurred periodically and persisted for three to four hours despite attempts to feed the infant, the symptoms probably being secondary to the air swallowing and hand sucking which resulted from inadequate feeding.

Six of the ten cases in this group were breast-fed infants who were being inadequately nursed. This is certainly the most common cause of colic in the breast-fed infant, of whom there were sixteen in our series. Illingworth,[2] in his excellent monograph on three-month colic, reports on fifty cases, including forty-four infants completely breast fed. In thirty-nine infants the symptoms of colic were eased by additional feeding.

The third group in this classification includes twenty infants (22.2 per cent) in whom the symptoms of colic were apparently related to the added carbohydrate in the formula. These infants were extremely susceptible to discomfort due to added carbohydrate in the formula and the symptoms could be reproduced at will by the addition of sugars to the feeding. The quantity of carbohydrate which had to be added to produce symptoms varied with each infant but was never above 1 ounce in a twenty-four-hour formula, and frequently was as little as ¼ ounce. In most instances the starch hydrolysates were used, Dextri-Maltose, Karo syrup, Dexin, Cartose, but rarely sucrose or lactose. In some instances more than one carbohydrate supplement was used at different times without any appreciable difference in the severity of the symptoms. It should be pointed out, however, that all milk mixtures contain lactose, and that some of the infants classified in the other groups (especially the psychosomatic) may have been reacting to this intrinsic carbohydrate.

The fourth group of this classification, butterfat intolerance, included ten infants (11.2 per cent). The following is an example of this group:

B. F., a white male full-term infant, both of whose parents manifested an unusual amount of anxiety and tension, developed colic at 3 weeks of age. The attacks occurred daily, persisting from four to eight hours every afternoon and evening, and were accompanied by severe cramps and the passage of much flatus. The original formula, evaporated milk, 9 ounces, water, 17 ounces, and Dexin, ½ ounce, was modified at 4 weeks of age by removing the Dexin. There was no change in the severity of the colic. At 6 weeks of age he was placed on 30 ounces per day of a half-skimmed powdered milk with ½ ounce of Dexin added. There was complete cessation of the colic until 8 weeks of age, when 3 ounces of evaporated milk was added to the formula, the amount of powdered milk being appropriately reduced. There was immediate recurrence of the colic accompanied by semiliquid stools. This formula was discontinued, and because he appeared hungry he was placed on Similac without any further episodes of colic.

Similac, Olac, Bremil, and many other modified milks have had the butterfat removed and vegetable oils substituted. They can therefore be used, provided the added carbohydrate does not disturb the infant. Recently a similar milk, without the added carbohydrate, was placed on the market and should be useful in these infants (Varamel).

The above case is an excellent example of the butterfat classification. It is again noted that a relatively small amount of butterfat reproduced the colic. It is possible that there might be some factor in the preparation of evaporated milk other than butterfat that induced the colic. For this reason Harris,[3] who had studied a large number of infants on whole milk and evaporated milk formulas, with and without carbohydrate, was asked to analyze his series in relation to the evaporated milk. He found no significant difference in the number of cases of colic in infants fed either evaporated or whole milk. This is in contrast to the decreased incidence of colic in those infants fed low carbohydrate feedings with either milk.

In the fat intolerance group, eight infants were on evaporated milk when the colic developed, the other two being on whole milk. When the latter were changed to evaporated milk the colic became worse. These ten infants were improved, however, when placed on half-skimmed powdered milk, half-skimmed whole milk, or a dilute evaporated milk formula with added carbohydrate and protein. It is extremely difficult to explain these cases, since in many instances the added evaporated milk did not increase the quantity of butterfat by more than 20 to 30 per cent, the formula used to correct the colic usually containing half-skimmed milk. It is probable that the type of fat and not the quantity is the responsible factor. One might assume that boiled milk contained fewer volatile fatty acids than evaporated milk, but of this we have no proof. At any rate, although the explanation is not readily arrived at, it seems clinically apparent that certain infants cannot tolerate any but the smallest quantity of butterfat. It should also be mentioned that none of the ten infants showed evidence of the celiac syndrome on follow-up examinations.

The fifth group in the series were nine infants (10 per cent) whose colic

was definitely on an allergic basis. All of these infants responded to the removal of milk from the diet and had other evidence of allergy, either atopic eczema, gastrointestinal symptoms from foods later in infancy, or a family history of allergy. Rosenblum and Rosenblum[4] suggested the examination of the stools for eosinophils as confirmatory evidence of gastrointestinal allergy. In a group of sixty infants with marked increase in stool eosinophils, 45 per cent manifested symptoms of colic. Nance[5] also found this procedure helpful. Unfortunately, we did not use this laboratory aid in our series.

It is generally assumed that allergic gastroenterospasm is a much more frequent cause of infantile colic than the 10 per cent found in our series. White[6] reported a series of seventy-seven infants with gastroenterospasm, 55 per cent of whom were on an allergic basis and were associated with atopic eczema. Clein[7] has analyzed 140 infants with allergy to cow's milk and found colic to be present in 29 per cent, with an additional 20 per cent showing marked restlessness.

In determining which infants were manifesting their symptoms on an allergic basis, the following factors were taken into consideration:

1. Satisfactory response to the elimination of milk from the diet.
2. Recurrence of gastroenterospasm on returning milk to the diet.
3. A family history of allergy.
4. Presence of other evidence of allergy, i.e., atopic eczema.
5. Persistence of allergy to milk beyond 3 months of age.
6. Evidence of allergy to other foods later in infancy.

Clein[8] found that in 71 per cent of one hundred allergic infants there was a family history of allergy. Kunstadter,[9] in a discussion of gastrointestinal allergy as a cause of the celiac syndrome, found that in 50 per cent of his allergic infants there was a family history of allergy, and that the same percentage also showed other manifestations of allergy. In view of these findings we believe a strong family history of allergy, and at least one of the last three items mentioned above, must be present before an infant can be classified in the allergic group. We do not feel that a satisfactory response to the removal of milk from the diet is sufficient evidence of allergy. Neither soy-bean milks nor amino acid milks contain butterfat and it is conceivable that an infant would respond well to these two milk substitutes, not because he had an allergic colic but because he fell into that large group which we have labelled as "fat intolerance." Furthermore, all of these infants were able to tolerate milk at 3 or 4 months of age, while some of those in the allergic group were 1 year of age before milk could be taken without serious consequences.

The sixth group in our series consisted of eight infants who obtained partial relief from their symptoms when added carbohydrate was removed from the formula, but required further assistance before their symptoms completely disappeared. In four of these infants hunger was the second factor (bringing to fourteen the total number in the hunger group): in one infant it was butterfat, and in three the second factor was never discovered.

There were also eight infants in the next group, the "unclassified group." These were cases in which,

although the symptoms disappeared promptly, it was not possible to place the infant in an etiological classification. Most of the infants responded to milk-free mixtures but failed to fulfill the requirements mentioned above for the allergic classification. We may, perhaps, be criticized for not including these infants in the allergic group. It can only be re-emphasized that a diagnosis of allergy is a permanent, almost lifetime diagnosis, and that the relief of gastroenterospasm by the elimination of milk from the diet is of itself not sufficient evidence for such a diagnosis.

The next classification to be considered is the miscellaneous group. There were four cases in this group, each one different from the other, but grouped together for the sake of convenience. The first of these illustrates the frequent association of orange juice and gastroenterospasm. Since this intolerance to citrus fruits seldom persists beyond 3 or 4 months of age and is so frequently seen in infants who have neither a family history of allergy nor other symptoms of allergy, and since skin tests rarely demonstrate an allergic state to the fruit, Glaser[10] feels that these infants should not be considered in the allergic group. This opinion is shared by McGee[11] and by Ratner and coworkers.[34]

The second case in this group illustrates the symptoms of colic produced by a tight anal sphincter or persistence of a partial proctodeal membrane. The third case in this series is one in which the symptoms of gastroenterospasm were apparently related to the consumption of an aqueous multiple vitamin preparation containing A, B, C, and D, and were reproduced when the vitamins were reintroduced at 6 weeks of age. The fourth and final case in this series is one in which the symptoms of colic were associated with constipation and were relieved when the latter was corrected. Although infantile colic is frequently associated with constipation, this was the only case in which it was felt that an etiological relationship existed.

There remains one group of infants, the second largest in our series, the "idiopathic or psychosomatic group." In these nineteen infants there was no reason to conclude that any idiosynerasy to any ingredient in the formula existed. Furthermore, the symptoms of gastroenterospasm persisted until the thirteenth week of age, and, in some instances, for an even longer period of time, despite any and all changes made in the management of these infants. There were three infants in this large group of unsuccessfully managed cases who appeared to be good candidates for infantile colic when first seen in the nursery at several days of age. It was noted at that time that these infants were vigorous hand suckers and this phenomenon continued to be a prominent feature of their behavior for the next three months. In our experience hand sucking is frequently seen in fretful infants, but in these particular infants it was so vigorous that the associated air swallowing was undoubtedly a primary factor in the production of the symptoms of colic.

It is unfortunate that none of these three infants was given a pacifier. Levine and Bell[12] reported on twenty-eight infants with typical symptoms of infantile colic, who were treated with a pacifier. All but three showed

a favorable response with prompt disappearance of the symptoms. Since the publication of Levine's paper we have tried a pacifier on many infants in whom the symptoms of colic had persisted, with some improvement in most cases.

It was, of course, found that not all of the infants in this last unsuccessful or psychosomatic group were hand suckers. In thirteen of these infants, however, it was observed that there was marked evidence of emotional instability on the part of the parents and it is believed that a thorough investigation of all of the nineteen families involved in this group would have revealed an even larger number in whom the psychosomatic factors were definitely pronounced, possibly suggesting a causal relationship to the colic manifested by the infants.

Table II. Age of Onset Relative to Clinical Classification of Infantile Colic

Classification	Age in weeks							Average	Total
	1	2	3	4	5	6	7		
Feeding technique	1		1					2.0	2
Hunger	2	4	3			1		2.5	10
Carbohydrate intolerance		6	8	4		1	1	3.25	20
Fat intolerance		3	7					2.7	10
Allergy		2	4	2			1	3.44	9
Carbohydrate intolerance plus a second factor		2	4	1	1			3.1	8
Unclassified		4	4					2.5	8
Miscellaneous		1	3					2.75	4
Psychosomatic	1	6	7	3	1	1		3.0	19
Total	4	28	41	10	2	3	2	2.92	90

DISCUSSION

In a survey of my private practice during a three-month period it was found that 5 per cent of the infants seen manifested the severe form of colic described above; another 10 per cent showed a nocturnal three- to four-hour period of restlessness which should be considered a milder form of infantile colic. Aldrich,[13] in a discussion of crying in the neonatal period, found that of forty-two infants observed by him only two (4.8 per cent) showed symptoms of colic. Keiter[14] found sixty-one cases of colic requiring treatment in a study of 275 consecutive infants seen in his private practice, an incidence of 22.1 per cent. Illingworth[2] found twenty-one infants with colic in a follow-up study of 100 infants in Sheffield, England; and Jorup[15] found 30 per cent among 589 children seen at a child welfare center in Stockolm. Although it is usually believed that infantile colic is not seen in institutions, Levin,[16] in a study of 645 infants under 3 months of age at the New York Foundling Hospital, found eight cases of severe infantile colic (1.3 per cent).

The average age of onset of symptoms for the ninety infants in our series was 2.91 weeks (Table II). In Illingworth's series,[2] however, where 88 per cent of the infants were breast fed, the onset of symptoms occurred before ten days in one-half of the series, and before fourteen days in all but six of the fifty infants. These infants were almost all breast fed, which fits in with the fact that in our series the onset was earliest in the breast-fed infants in the hunger

series. Pierce[17] found that in premature infants the age of onset was usually two weeks plus the duration of the prematurity. In the present series of ninety infants, there were two premature infants. The first, born at thirty-seven weeks of gestation, showed the early symptoms of colic at five weeks of age; the second, born at thirty-six weeks of gestation, showed his first symptoms at four weeks of age. Obviously two cases cannot be used as evidence that Pierce's observations were incorrect. only 56 per cent had no sibling, 35 per cent had one, and 9 per cent more than one.

The relationship of breast feeding to the frequency of infantile colic is argumentative. It is our impression, however, that an infant being fed an "adequate" quantity of breast milk is not likely to develop colic. There were five completely breast-fed infants in this series. Three of these developed colic because of underfeeding, another possibly on the basis of allergens transmitted via the breast

TABLE III. INFANTILE COLIC: ANALYSIS OF SIBLING RELATIONSHIP AND PREVIOUS CASES OF COLIC IN FAMILY

	NUMBER OF SIBLINGS						
		ONE		TWO		THREE	
CLASSIFICATION	NONE	WITH COLIC	WITHOUT COLIC	WITH COLIC	WITHOUT COLIC	WITH COLIC	WITHOUT COLIC
Feeding technique	2						
Hunger	7		3				
Carbohydrate intolerance	14	1	2	1	2		
Fat intolerance	7	2	1				
Allergy	4		3	1	1		
Carbohydrate intolerance plus a second factor	5		2				1
Unclassified	7		1				
Miscellaneous	3		1				
Psychosomatic	14	1	4				
Total	63	4	17	2	3	0	1

Since the entire family is involved in the raising of an infant, and the parents' attitude is considerably influenced by the number of other children in the family, the sibling status of each infant with colic was examined (Table III). It was found that sixty-three (70 per cent) of the ninety infants were firstborn, twenty-one (23 per cent) had one sibling, five (5.6 per cent) had two, and one (1.4 per cent) had three. In comparison with a group of fifty-eight infants picked at random from my practice, it was found that infantile colic is more common in the smaller family, since in the control group

milk, and in one case no explanation for the symptoms could be found. Higgins[18] and Rosamond[19] agree that colic in a breast-fed infant is usually due to underfeeding.

A study of the pediatric literature of the past forty years indicates that there are many theories regarding the etiology of infantile colic. Gordon[20] presents an excellent review of the past and present as related to the "hypertonic infant." An attempt was made to evaluate some of our infants by Gordon's standards. It was found that during the period of colic, almost all of the infants appeared hypertonic, but only in a small

percentage did this persist between episodes of colic. Hild[21] came to the same conclusion. Furthermore, in our experience it was rare to find colic associated with vomiting, usually considered the most common symptom of the hypertonic infant.

There are, of course, many different theories as to the mechanism by which the hypertonicity is produced. One large group believes that it is due to an imbalance of the autonomic nervous system, producing the "vagotonic" baby, and that the pylorospasm and gastroenterospasm can readily be relieved by atropine.[22, 33] Another viewpoint is mentioned by Ivy[24] who, in discussing gastrointestinal hypertonicity in the normal infant, refers to Zamorani's[25] unconfirmed observations that the celiac ganglion is not histologically completely mature until 2 years of age.

The psychosomatic approach to the hypertonic infant is certainly not new, but in the past twenty years the number who support this as the major factor in infantile colic has greatly increased. In 1934, Zahorsky[26] pleaded for the return of the cradle, pointing out that rocking after feeding aided in the digestion and absorption of the formula and decreased the incidence of enterospasm. Holt[27] pointed out the satisfactory results frequently obtained by substituting a calm nurse for an agitated mother. Shawkey[28] carried the psychosomatic case a bit further by calling attention to the fact that the number of hypertonic infants increased fortyfold from 1916 to 1935 due to the increased pace of civilization. In fact, most of the recent literature on the hypertonic infant emphasizes the psychosomatic or emotional theory. Keiter,[14] Hild,[21] Moore,[29] and Neff,[30] however, include the psychosomatic as only one of the many factors which contribute to the symptom-complex of infantile colic.

As far back as 1915, Klose[31] pointed out that infantile colic in the hypertonic infant was frequently due to the feeding of improper milk mixtures or to faulty feeding techinques. Grulee[32] in 1924 discussed formulas high in carbohydrate and butterfat and their relationship to infantile colic. Higgins[18] agreed that colic in artificially fed infants was generally due to an excess of carbohydrate or butterfat, but rarely to the protein. He advocated increasing the protein and decreasing the carbohydrate and butterfat in the formulas. These authors support our concept that colic is frequently due to the inability of the infant to tolerate butterfat and carbohydrate. It is our opinion that there are many infants who can tolerate these components of the usual formula only in greatly reduced amounts, while others have difficulties with even minimal quantities. In our experience the best results in the management of infantile colic have occurred when the emphasis was placed on the ingredients and administration of the formula, rather than on the emotional reactions of the parents.

TREATMENT

It is apparent, therefore, that the treatment of infantile colic should be directed toward the elimination of the etiological factor rather than the direct attack upon the resultant gastroenterospasm. It has been our practice to check the feeding technique immediately and to eliminate

this as a possible factor. In recent months several new nursing bottles have appeared on the market. In some instances, a change from one to another has proved beneficial, but we have been unable to draw any conclusion as to the efficiency of any particular type of bottle. It still appears that the technique of infant feeding, and not the bottle used, is the more important factor in the prevention of infantile colic.

Since we agree with Illingworth[2] that overfeeding rarely causes trouble, we have urged our mothers to offer larger quanties of formula to eliminate the possibility of hunger playing an important role in the production of colic. In many instances it has been observed that only when cereal was added to the diet did the symptoms disappear.

In all cases, furthermore, time was taken to reassure the parents as to the good health of their infant, and to explain the nature of infantile colic to them. We feel that in many instances more can be accomplished by making a visit to the home than by attempting to treat the infant at a routine office visit.

In addition to the measures mentioned above, it has been found helpful in occasional instances to elevate the head of the crib in order to increase the efficiency of "burping," as advocated by Snow.[33] It is also our custom to use certain measures during the acute attack of colic. These include heat and massage to the abdomen, rectal glycerin suppositories or small enemas, and mild sedatives such as phenobarbital sodium by mouth. The effectiveness of these measures is doubtful, but many parents feel that the infant is improved by them. The recent reintroduction into American medicine of the pacifier adds another controversial factor to the large group of remedies for infantile colic.

CONCLUSION

Infantile colic is a common clinical entity which cannot be ignored. It is seen frequently in private practice and somewhat less frequently in clinics and institutions. Although emotional and environmental conditions play a large role in the production of this symptom-complex in some infants, there are many more in whom poor feeding technique, underfeeding, allergy, or an idiosynerasy to carbohydrate and butterfat seem to be etiological factors. In these latter, much can be accomplished by close observation of the feeding technique and changes in the basic ingredients of the formula. Although these observations are not new, they have not received the proper emphasis in pediatric teaching in recent years. Every case of infantile colic should be considered with this approach in mind, and only those who fail to respond may be classified in the psychosomatic group.

SUMMARY

Ninety cases of infantile colic were studied in detail and classified as follows:

1. Poor feeding technique, 2 per cent.
2. Hunger or underfeeding, 11 per cent.
3. Carbohydrate intolerance, 22 per cent.
4. Fat intolerance, 11 per cent.
5. Allergy, 10 per cent.
6. Carbohydrate intolerance plus a second factor, 9 per cent.

7. Unclassified and miscellaneous, 13 per cent.

8. Psychosomatic group, 22 per cent.

The part played by each of these factors is discussed. The role of allergy, carbohydrate, and fat intolerance is emphasized.

A program for the proper approach to an infant with infantile colic is outlined.

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WOLFF-PARKINSON-WHITE SYNDROME

Report of Two Cases in Infants

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PROLONGED duration of the QRS complex, short P-R interval, and unchanged P-J interval, frequently associated with attacks of paroxysmal tachycardia, known as Wolff-Parkinson-White syndrome,[1] occurring in otherwise healthy adolescents has been reported in infants.[2-13]

These patients were from several days to one year of age. Eight were males,[2, 3, 5, 8-12] and four, females.[4, 6, 7, 13] All have had episodes of paroxysmal tachycardia. Five have not shown reversal to normally shaped complexes,[2, 4-7] and one case was associated with coaretation of the aorta[11]; the patients in two cases reported died in heart failure after an attack of paroxysmal tachycardia[2, 3]; there was no autopsy in one case, and accessory muscular connections between auricle and ventricle were found on autopsy in the other case.[3]

CASE REPORTS

Case 1.—G. C. was a normal, full-term male infant, delivered spontaneously at Queens Memorial Hospital on Feb. 15, 1955. The birth weight was 9 pounds 2 ounces and physical examination at birth and on discharge was within normal limits. At the age of 3 weeks the patient developed short episodes of cold perspiration, mostly at night, lasting ten to fifteen minutes. During the last episode, the night prior to the admission, the patient turned suddenly pale, with a slight bluish tinge, and became dyspneic. The infant was, therefore, hospitalized on Feb. 21, 1955, at the age of 5 weeks.

Physical Examination.—The patient was a well-nourished and well-developed white male infant who appeared acutely sick; his color was pale, with slight cyanosis of face and extremities. Respirations were labored at a rate of 36 per minute with subcostal retractions. Temperature was 103.4° F. and pulse rate 160 per minute. Weight was 11 pounds 12 ounces. Auscultation of the lungs showed crepitant, inspiratory râles in both lung bases posteriorly, more marked on the right. The heart was not enlarged and no thrills were felt. The liver was three fingerbreadths below the costal margin and there was no peripheral edema. The only other finding on physical examination was a slightly reddened pharynx with mucous exudate.

Laboratory Findings.—Chest x-ray on admission revealed no pulmonary congestion and heart was normal in shape and size. The hemoglobin was 15.0 grams per 100 c.c.; white blood count was 14,600 with normal differential count for age; urinalysis was normal. An electrocardiogram the next day revealed the characteristics of Wolff-Parkinson-White syndrome: P-R interval of 0.06 to 0.07 second, QRS interval of 0.07 to 0.08 second, delta wave in L_2 (Fig. 1); fluoroscopy of the heart in anteroposterior, oblique, and lateral views revealed no abnormalities. Blood pressure readings

From the Pediatric Division, Queens Hospital Center, Dr. Meyeron Coe, Director.

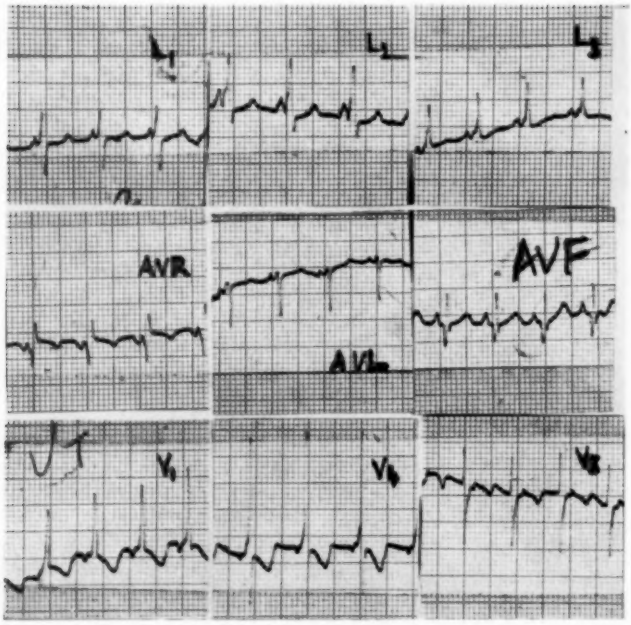

Fig. 1.—Regular sinus rhythm at 150 per minute; P-R interval 0.06 to 0.07 second; QRS interval 0.07 to 0.08 second; P-J interval 0.14 second; inverted T waves in V_1, V_4, and V_5; right axis deviation; delta wave in L_c. Wolff-Parkinson-White syndrome.

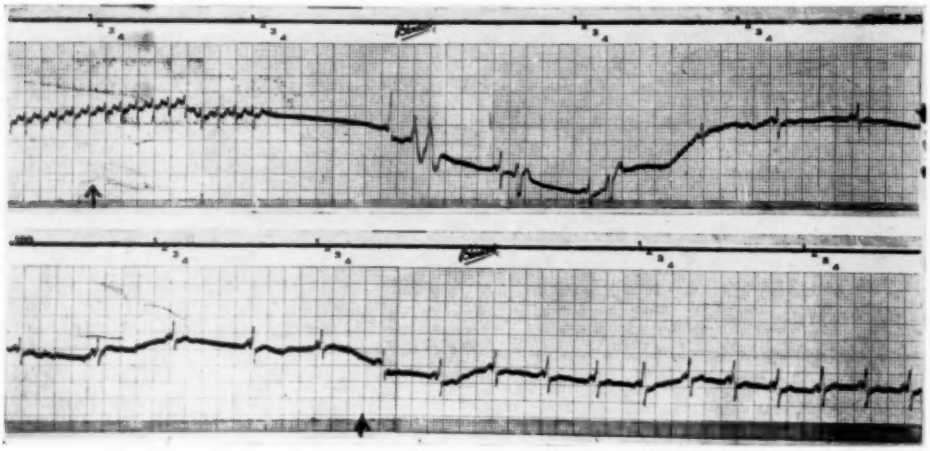

Fig. 2.—Record taken during an attack of paroxysmal tachycardia; first standard lead. At the first arrow supraorbital pressure was applied. Two seconds later an asystole of one and one-half seconds' duration occurred, followed by several ventricular premature contractions, some of them coupled with normally shaped QRS complexes, which were followed by sinus rhythm at a rate of 60 per minute; at the second arrow supraorbital pressure was discontinued and shortly afterward the rate decreased to 115 per minute.

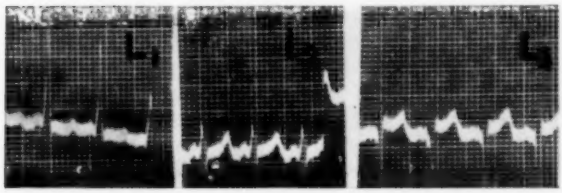

Fig. 3.—Regular sinus rhythm at 150 per minute; P-R interval 0.06 to 0.07 second; QRS interval 0.07 second; P-J interval 0.13 second; left axis deviation; Wolff-Parkinson-White syndrome.

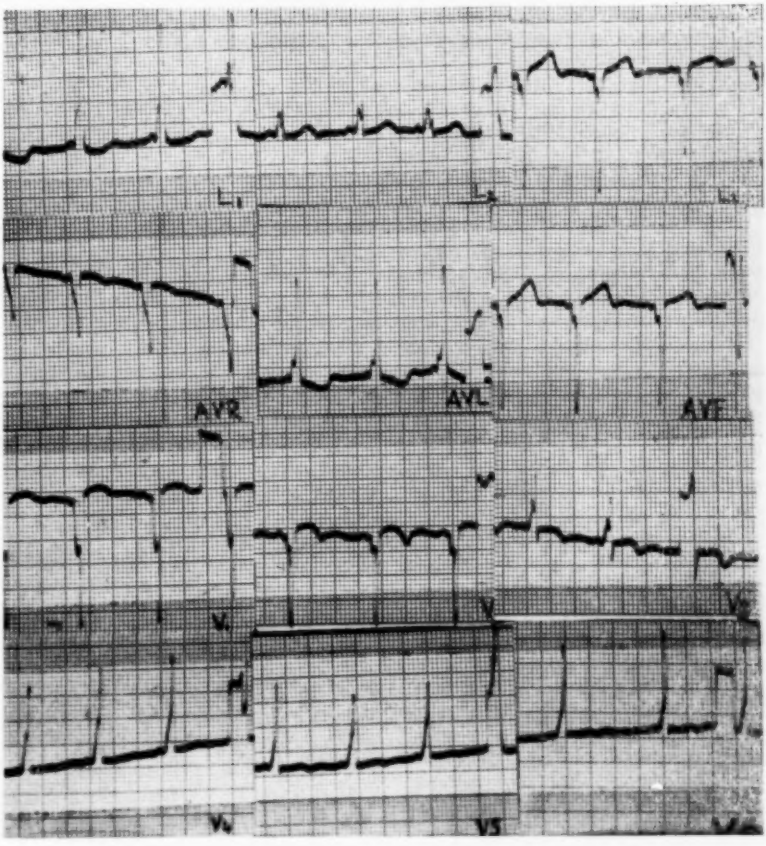

Fig. 4.—Regular sinus rhythm at 86 per minute; P-R interval 0.07 to 0.08 second; QRS interval 0.08 to 0.09 second; P-J interval 0.12 second; left axis deviation; Wolff-Parkinson-White sydrome; delta wave seen in all leads. Record almost identical with the first one, made three and one-half years ago at the age of 1 month.

were: left arm, 84/52; right arm, 82/50; left and right thighs, 90/?. The basal râles, dyspnea, slight cyanosis, and hepatomegaly suggested the diagnosis of heart failure.

Course.—The patient was given 0.1 mg. of Digoxin every six hours for four doses, followed by 0.03 mg. daily. During the next two to three days the symptoms of heart failure gradually disappeared and heart rate remained between 116 and 155 per minute. On his eighth hospitalization day there was a sudden relapse of generalized cyanosis, of marked degree this time, with labored respirations, 42 per minute. At that time the heart rate was found to be too rapid to be counted and an electrocardiogram revealed supraventricular tachycardia with a rate of 295 per minute. Unilateral supraorbital pressure was applied and the heart rate dropped to 115 per minute (Fig. 2). Shortly afterward cyanosis and dyspnea disappeared. Daily dose of Digoxin was increased to 0.04 mg. per day. The patient has had three more attacks of paroxysmal tachycardia, which were promptly relieved by unilateral supraorbital pressure, on the tenth, thirteenth, and seventeenth hospitalization days. Later Digoxin dosage was gradually decreased and was discontinued on the twenty-eighth day of hospitalization. The patient remained asymptomatic and was transferred to a home on the thirty-sixth hospitalization day.

Case 2.—E. G., a Negro female infant, was referred to our outpatient department on Nov. 16, 1951, at the age of 1 month, because of persistent tachycardia. On physical examination the heart rate was found to be regular, 151 per minute, the left eardrum was injected, and the pharynx was reddened. The remainder of the physical examination was within normal limits. The diagnosis of left catarrhal otitis media was made and the infant was treated successfully with penicillin therapy. An electrocardiogram on November 23 revealed the characteristics of the Wolff-Parkinson-White syndrome (Fig. 3). An x-ray of the chest on November 27 revealed the heart to be of normal contour and size. The patient has been seen periodically in the cardiac clinic ever since, has developed normally, and no further episodes of tachycardia have been observed. Repeated chest x-rays remained within normal limits and the electrocardiograms (January, March, August, 1953, and July, 1955) remained essentially unchanged (Fig. 4).

COMMENT

Perhaps the most widely accepted etiology of the syndrome involves the presence of an accessory conducting pathway between the auricle and the ventricle. Kent[15] has shown that direct muscular connections between the auricle and the ventricle occur in certain animals. Butterworth and Poindexter[16] produced electrocardiographic tracings characteristic of the Wolff-Parkinson-White syndrome in dogs by creating an artificial short-circuit between the auricle and the ventricle. Histologically, such muscular connections were demonstrated by Wood and co-workers,[14] and in the case of Kimball and Burch.[3] The Wolff-Parkinson-White syndrome is rarely associated with other congenital anomalies.

Clinically, an attack of paroxysmal tachycardia is accompanied by sudden change in color, perspiration, and is associated with irritability and, rarely, vomiting; these symptoms may subside spontaneously or persist for hours or even days, in which case symptoms of cardiac failure may appear. Rapid heart rate and typical electrocardiographic changes after the attack is terminated provide the clue for diagnosis.

In the treatment of an attack, digitalization appears to employ the drug of choice. Procaine amide, neostigmine methylsulfate, or acetylcholine bromide has also been found effective. In our case, the supraorbital pressure applied unilaterally has promptly terminated the attacks.

SUMMARY

Two cases of Wolff-Parkinson-White syndrome with paroxysmal tachycardia in infants are presented: the first was in a 5-week-old male infant who was treated with digitalis, and the attacks were arrested by unilateral supraorbital pressure on four occasions; the second occurred in a 1-month-old infant in whom the tachycardia subsided spontaneously, and whose case was followed for four years.

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Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
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CLINICAL HISTORY

THIS 7-year-old child was well until six weeks before her death, when she developed a low-grade fever, sore throat, and mild headache. Two of her siblings developed tonsillitis at the same time. All three children were given oxytetracyline for two days and thereafter were well. Fourteen days after onset of symptoms, the patient began to limp and complain of pain in the left ankle.

The family physician then made the following observations: The child's temperature was 101° F., and her pulse was 130 per minute. Examination of the heart revealed a Grade 2 apical systolic murmur. The right knee was hot and swollen. The patient was admitted to a hospital where an electrocardiogram showed a P-R interval of 0.20 second. Laboratory examinations there revealed a sedimentation rate of 32 mm. per hour, a blood hemoglobin of 9 grams per cent, an erythrocyte count of 3.65 million per cubic millimeter, and a leukocyte count of 5,950 per cubic millimeter with a normal differential count. The patient was treated with aspirin every three hours and the temperature became normal within three days. The patient was hospitalized for ten days and transferred to the House of the Good Samaritan of The Children's Medical Center, with a diagnosis of rheumatic fever.

The past history was uneventful except for prematurity of three weeks; the birth weight was 4 pounds 2 ounces, and there was an uneventful neonatal period. The child always seemed thin and had "more fevers" than the siblings. She had measles and mumps prior to age 5, and an uneventful DPT and vaccinia immunization.

The family history revealed that a paternal aunt had rheumatic fever at age 9, and now has rheumatic heart disease. The paternal grandmother has had heart disease for twenty years, and this is now associated with asthma.

On admission, the girl's temperature was 99.6° F., the pulse 112 per minute, respirations 24 per minute, and blood pressure 95/55 mm. of mercury. The weight was 41 pounds. The child was thin, listless, and pale. The tonsils were large and almost met in the midline. There were small palpable anterior cervical nodes. The heart was enlarged 1.5 cm. beyond the midclavicular line. There was a

Grade 3 apical blowing systolic murmur which transmitted well to the axilla and to the right and left lung bases. There was a Grade 2 apical mid-diastolic rumble. The pulmonary second sound was moderately accentuated. There was an apical gallop. The liver was palpable 2 cm. below the right costal margin and was not tender.

Initial laboratory examinations showed the corrected sedimentation rate to be 20 mm. per hour, the hematocrit 33 per cent, the hemoglobin 12 grams per cent. The urine was normal. A throat culture was negative for beta hemolytic streptococci. The antistreptolysin titer was positive at a dilution of 1:250. The electrocardiogram had a slightly prolonged P-R interval (0.16 second, against a normal of 0.14 second for the heart rate and age). A chest roentgenogram revealed definite enlargement of the heart with a configuration suggesting mitral valvular disease. There was a moderate degree of pulmonary vascular congestion.

The patient was started on cortisone, 300 mg. daily, which was continued for three weeks. She received potassium chloride, 3 Gm. a day, a low-sodium diet, and oral penicillin, 200,000 units twice daily.

On the fourth hospital day, she received 1.3 c.c. of gamma globulin because of exposure to infectious hepatitis. By the end of the third week, a slight but definite "mooning" of the face and acne had appeared. Her weight increased to 52 pounds. Fourteen days after her admission, a patient in the room across the hall developed chicken pox. Seventeen days later, the patient developed lesions on the abdomen and chest which were erythematous and 2 to 3 mm. in diameter, but not raised. The patient simultaneously complained of intermittent abdominal pain which was quite vague and was referred to the umbilicus. The abdomen was completely relaxed, without suggestion of tenderness. The next day, the patient began to complain of more severe abdominal pain and refused to eat. There was moderate voluntary spasm and suggestive tenderness in the right paraumbilical region. The temperature was normal. At this time the peripheral leukocyte count was 21,700 per cubic millimeter, with a differential count of 50 per cent polymorphonuclear cells, 12 per cent immature polymorphonuclear cells, 28 per cent lymphocytes, 8 per cent monocytes, and 2 per cent eosinophils. The urine examination was normal.

By the afternoon of the same day, abdominal pain had increased in severity and was associated with considerable spasm in all areas and generalized tenderness. Peristalsis was present and was considered normal. A rectal examination was negative. Cardiac findings had not changed since admission. The systolic blood pressure was 140 mm. of mercury and the diastolic pressure ranged from 90 to 110 mm. of mercury. The skin lesions developed definite vesicular centers, and a single vesicular lesion was present on the palate. A day later the patient became febrile, with a temperature of 100° F. and a pulse of 110 per minute. The child seemed somewhat lethargic and the abdominal findings were unimpressive. Peristalsis was now hyperactive. The patient had been maintained on fluids by mouth, barbiturates, and codeine as needed. The afternoon of this day,

the patient suddenly vomited some brownish material and shortly thereafter became completely unconscious. The pulse was rapid, and the respirations shallow, irregular and very slow. Cyanosis developed rapidly despite suctioning, intravenous caffeine and nasal oxygen. The blood pressure was now 140/100 mm. of mercury. At this point the skin lesions were noted to become hemorrhagic. Though the patient at first was quite flaccid and no convulsive movements were noticed, she developed generalized rigidity and mild twitching of the hands within fifteen minutes. She remained moderately cyanotic with shallow, irregular respirations and heartbeat exceeding 200 for approximately one-half hour. At that time, an endotracheal tube was inserted. With intermittent oxygen she became pink and almost simultaneously developed generalized convulsive movements. The blood pressure at this time was unobtainable and no pulses were palpable. An intravenous infusion was started with noradrenaline. Thiopental (2 c.c.) controlled the convulsion and there was a prompt response in the blood pressure, which was maintained subsequently at approximately 100/70 mm. of mercury. Up to this point, the patient's abdomen had been distended and markedly tympanitic. With the rise in blood pressure, the patient passed a stool of brown feces with associated red blood and mucus surrounding the stool. Shortly thereafter, a large, bloody, liquid stool was passed. An intravenous infusion of 250 c.c. of plasma followed by compatible blood was given. A lumbar puncture was performed, which revealed a normal pressure and clear fluid. The cerebrospinal fluid contained 2 lymphocytes per cubic millimeter, 30.5 mg. per cent of protein and the Pandy reaction was negative. The peripheral leukocytes now numbered 30,000 per cubic millimeter, with a differential of 50 per cent polymorphonuclear cells, 45 per cent lymphocytes, and 5 per cent monocytes. There were adequate platelets on smear. The bleeding and clotting times were normal.

Penicillin and streptomycin were started and cortisone was continued. When the convulsions subsided, the patient developed spontaneous irregular respirations. She continued to have large, foul-smelling, bloody black stools and remained deeply comatose. The eye grounds were normal. Levin suction of the stomach produced small amounts of bloody mucus. Approximately twelve hours after initial unconsciousness, the patient began to exude frothy blood from the endotracheal tube. Coarse râles appeared in all areas of the chest. The blood pressure dropped steadily despite forced blood infusions by two routes. Respirations became very irregular and heartbeat extremely rapid and faint. Respirations and heartbeat ceased approximately twelve hours after onset of coma.

DISCUSSION

DR. EDWARD H. KASS.*—I think the first thing to note is that there was probably a family outbreak of streptococcal infection and that the patient was inadequately treated. The problem of the practitioner who must take cultures is a difficult one and I am completely convinced that until some

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means are set up whereby the practitioner can culture all patients with sore throats, and all members of families in which a sore throat has appeared, there will be no real solution to the present problem.

DR. LOUIS K. DIAMOND.—What means do you refer to, Doctor?

DR. KASS.—In this state one need only take the culture, put it in the mail, and wait for the report. Communications are such that within twenty-four hours cultures generally arrive at the appropriate laboratory. The big delay seems to be in getting the answer back by mail, but a telephone call usually solves that, and within forty-eight hours from the time the culture is taken (except for week ends) anyone working in the Boston area can determine whether or not streptococci are present. This, of course, has all kinds of obvious advantages. An easy way to handle sore throats, in the home, is to start the patient on penicillin and within forty-eight hours one decides whether to continue therapy. Obviously, if streptococci are present, one must continue treatment for a minimum of a week, preferably for ten days. If no streptococci are present there is no need to continue antibiotic therapy unless there are other strong clinical indications that the culture was incorrect. The use of repository benzathine penicillin that gives detectable blood levels for a week has come into prominence lately. I think, to most of us who have seen an unusual number of reactions to this drug, this prolonged action appears to be a mixed blessing. The reaction rate continues to be higher than with other forms of penicillin, with a high incidence of serum sickness-like responses.

In any event, in this patient there seems little doubt that a streptococcic infection was present, was inadequately treated, and that the patient developed acute rheumatic fever.

Nosocomial infections are an increasing problem in the field of infectious disease. We are seeing increasing numbers of staphylococcal infections in hospital populations. Patients with infections of the urinary tract seem to have species of gram-negative rods characteristic of particular hospitals. We have now enough evidence of hospital-acquired infections to make the hospital not an entirely blameless place.

In this case the problem that arose was the development of varicella in the hospital. The patient was given cortisone, which was begun at a level of 300 mg. and then decreased to 250 mg. I think the fact is well established that a dose of cortisone smaller than 300 mg. a day seems to have no more important effect than aspirin on the clinical course of acute rheumatic fever. What the 300 mg. dose level will do remains to be seen. In any event, this patient developed hypercorticalism, suffered an exposure to varicella, and then developed varicelliform lesions. From the description, one would have little reason to doubt that these were varicelliform; they came on at exactly the right time, went through the course of developing vesicular centers, and there was even a lesion on the palate. The difficulties were twofold: first, these became hemorrhagic, which is unusual in varicella, and, second, the patient developed encephalitic signs.

That encephalitis was present is evident on purely clinical grounds, for there were lassitude, lethargy, vomiting, tremors, and changing consciousness. The encephalitis came on at the expected time. Most encephalitis secondary to varicella comes on sometime between three and seven days, but there are authentic instances in which the encephalitis preceded the eruption, and there are cases in which the encephalitis appeared on the first day or second day after the eruption. The absence of cerebrospinal fluid findings is somewhat disturbing, but in every series of cases of encephalitis secondary to varicella, there have been a number of patients who have not had important changes in the spinal fluid. Pleocytosis and a small increase in protein are perhaps the most important findings, but here there was no clear evidence of changes in the spinal fluid. In the presence of cortisone, perhaps the entire inflammatory response of the central nervous system was suppressed, so that one could not be certain of the cerebrospinal fluid pattern as a diagnostic aid.

In addition, the patient developed confusing abdominal symptoms. These consisted of a series of painful, nonobstructive episodes, with hyperactive peristalsis, and, later, distention and tympany.

I think I can illustrate the overwhelming difficulties that one must face in the cortisone-treated patient with just two simple case reports: one, the case of a 16-year-old patient with lobar pneumonia who was given ACTH, and no antibiotics.[1] This patient promptly became afebrile and asymptomatic, but maintained his bacteremia for some forty-eight hours after he became afebrile. At the time he was bacteremic he felt well enough to ask if he could be discharged from the hospital, so that he could attend National Guard drill. Equally pertinent is Dr. Kinsell's case of a 5-year-old boy who had evidence of generalized peritonitis, secondary to perforated appendix. This patient had abdominal distention, rigidity, and absent peristalsis. The patient now had virtually no pain in his abdomen, and ACTH was stopped; within hours, all the classic evidence of peritonitis returned. ACTH was given again, and everything disappeared again. ACTH was again stopped, surgery was performed, and the patient was found to have a perforated appendix with peritonitis. This emphasizes that the adrenocortical hormones are extraordinary substances, in terms of their capacity to alter the classical pictures of disease as we have learned them.

I think the most important diagnostic possibility is that this child had acute, generalized varicella. This, of course, is extraordinarily rare. There are only a few fatal, autopsied cases of varicella. This child did have cortisone, and we know that the effect of cortisone and of hydrocortisone has been to increase the susceptibility to bacterial, viral, protozoan, helminthic, and fungal infections.[2] One of the simplest ways to observe this in a dramatic fashion is to induce herpes simplex infection in the eye of the rabbit; the cortisone-treated animal develops a fulminant infection that shows remarkably little inflammatory response, exactly as one would expect with a great, spreading, ulcerative eye lesion. The animal not treated with cortisone customarily develops a mild keratitis that disappears in a few days.

We can postulate, then, that the ordinary defensive mechanisms were not operative in this case and therefore a much more severe form of varicella appeared. We already know from autopsy and available clinical data that varicella is a generalized infection; in the few autopsied cases, lesions have been found in the esophagus, renal tract, adrenal glands, liver, kidney, and brain. There is ample evidence that there must be a stage of viremia. The fact that hemorrhagic lesions appeared in this case might also be consistent with a severe varicella infection. Dr. Shwachman told me about the observations he has been making on children with leukemia who developed an unusually severe form of varicella with widespread, disseminated, hemorrhagic lesions, which would also suggest that host-defensive mechanisms were inoperative. Some of these patients were treated with cortisone. We may assume that the varicelliform lesions, instead of stopping at the esophagus, appeared along the gastrointestinal tract, involving the mucosa of the intestinal tract below the stomach.

The other possibility that stands out is that there was some other abdominal catastrophe, and, of course, appendicitis comes to my mind first. There is a great deal of discussion in the literature of the coincidence of appendicitis in varicella. The studies by Lawrence and Waring[3] from the Haynes Memorial Hospital a few years ago indicated rather strongly that there was not actually an increased incidence of appendicitis in children with varicella or other exanthems. In this patient, the possibility must be considered that appendicitis appeared—whether secondary to the varicella is relatively immaterial—and that the characteristic, clinical findings were obliterated by the coincident administration of cortisone. I know no way out of this dilemma at this time. We cannot rule out other catastrophies, such as perforated viscus, Meckel's diverticulum, etc., but there is no positive evidence for invoking any one of these conditions in this case.

We cannot rule out some unrelated secondary disease, such as subacute bacterial endocarditis, except, again, we have no positive evidence to suggest it. It is interesting that in the few cases of subacute bacterial endocarditis that have received cortisone, the same thing has happened as has happened in patients with pneumonia—the fever tends to go away, the patient feels much better, but the positive blood cultures and the peripheral embolization go on pretty much unchanged.

Another possibility that one might consider is disseminated streptococcal infection. The patient was not treated with large doses of penicillin, until terminally. Extirpated tonsils may contain *beta* hemolytic streptococci after the throat cultures have become free of these organisms. The possibility ought to be considered that cortisone sufficiently depressed the patient's resistance to permit a streptococcus to break out and become a disseminated infection. This is not likely, however, in view of the fact that the patient had received penicillin throughout the hospital stay. By the same token, we might consider briefly the possibility that a disseminated staphylococcal infection

occurred. We have seen this with remarkable frequency. I was at a hospital in another city just yesterday to see a patient who had received cortisone, developed a disseminated staphylococcal infection and, among other things, sloughed three feet of his jejunum or ileum. That is a very real and not infrequent complication of the administration of cortisone. I should like to know whether the Gram stains of the stool showed any predominance of staphylococci.

DR. DONALD C. FLYER.—The stool smear was not done, but culture of the stool showed *Escherichia coli.*

DR. KASS.—In summary, I think this child had an extremely severe form of varicella, accompanied by encephalitis and presumably disseminated lesions elsewhere. I would invoke the possibility that there were lesions in the gastrointestinal tract to account for the terminal bleeding.

DR. CHARLES JANEWAY.—The only thing, I think, that would be worth adding is that we have had a fair number of individuals who have had either cerebral tumors or central nervous system infections, who have developed ulcerations in the gastrointestinal tract. I wonder here, with the shock so prominent, whether there wasn't varicella involvement of the brain stem and, with that, ulceration of the gastrointestinal tract and bleeding developed.

DR. DIAMOND.—How much blood was given, Dr. Fyler?

DR. FYLER.—About 1,500 c.c.

DR. DIAMOND.—And the hematocrit, or red count, hemoglobin was very satisfactory?

DR. FYLER.—Again, toward the end, I have no idea.

DR. RANDOLPH K. BYERS.—I would agree with Dr. Kass that if a streptococcus was present in the throat, a day or two of antibiotic therapy would probably do no harm. But I am sure we have seen deaths that might have been prevented when patients harboring other more resistant organisms were given a day or two of therapy. Recently, a child in the hospital was given antibiotics a few days for fever, the etiological agent of which was not identified. The child, I am sure, had a meningitis from the beginning. After the antibiotics were withdrawn the meningitis flared up, and this child has had a very poor result from his influenzal meningitis. One must try to be accurate in diagnosis and maintain treatment until the child is thoroughly over his infection, and this usually takes around a week.

DR. CANNON ELEY.—I saw this patient one night with Dr. Massell and Dr. Fyler, and the clinical condition couldn't be any more clearly described than it is here. The patient was desperately ill, and we were quite apprehensive about the other patients in the same rheumatic fever ward who had been on cortisone. My feeling was that the melena was secondary to varicella ulceration along the bowel. We also entertained the idea that Dr. Janeway mentioned—that this could be due to the central nervous system involvement. Our dilemma at the time was that if we stopped the cortisone we could get into problems of adrenal insufficiency, or whether we should run the risk of carrying on the cortisone, hoping to

cover the patient with antibiotics. It was really a problem. There have been cases reported of varicella with no particular medication in which large hemorrhagic lesions have occurred. They may have simply had a true atypical symptomatic purpura.

DR. JANEWAY.—Dr. Eley, do you think we can dismiss the encephalitis on the basis of lumbar puncture? The hospital record states that shortly before death the spinal fluid had a normal pressure and was clear, though 2 lymphocytes per milliliter were found.

DR. ELEY.—Not by any means. We see that quite often, especially in people with poliomyelitis who come in with a normal spinal fluid. If this patient had lived long enough, there may have been an increase in the protein. I don't think the absence of cellular elements rules out encephalitis. I think the child did have a varicella encephalitis.

DR. CHARLES V. PRYLES.—I should like to give a dissenting opinion regarding the diagnosis of encephalitis. Dr. Denny-Brown is continually pointing out that the diagnosis of encephalitis should not be made in the absence of alterations in the lumbar fluid. In the absence of pleocytosis and any chemical changes one should be very cautious about making the diagnosis of encephalitis in this patient. Cortisone, as Dr. Kass suggested, may have so depressed inflammatory changes in the brain that no cytologic change occurred. But I think the protein might be expected to be elevated. I would be a little reluctant to accept the diagnosis of encephalitis.

DR. DIAMOND.—Was that observation based on single samples?

DR. BYERS.—One sample.

DR. KASS.—In a study by Appelbaum and co-workers[4] of thirty-five autopsied, proved cases of encephalitis, a number had no important change in the spinal fluid.

DR. WILLIAM B. CHEATHAM.—At autopsy this child was moderately well developed and well nourished; there was definite hirsutism and Cushing's facies. Blood was exuding from the mouth and nose and there were several vesicles on the buccal mucosa. There were slight abdominal distention and clubbing of the fingers and toes. The rash was maculopapular to vesicular, and this was moderately prominent over the head, the neck, the trunk, and the thighs, but was not seen over the distal part of the extremities to any extent. The skin lesions were characteristic of one of three diseases which are, actually, microscopically indistinguishable. These are varicella, herpes zoster and herpes simplex. However, the skin lesions do show certain characteristics which are a bit out of the ordinary; those are such as would indicate that this was a very fulminant disease and that it probably was widespread infection. In the dermis one could see extensive hemorrhage with inclusions in the fibroblasts as well in the capillary endothelial cells. The epidermis had swelling and ballooning of the epithelial cells, with formation of small vesicles (Fig. 1). In the bases of these vesicles, of course, one could see numerous intranuclear inclusion bodies, and this is a bit different from the usual varicella lesion, in which

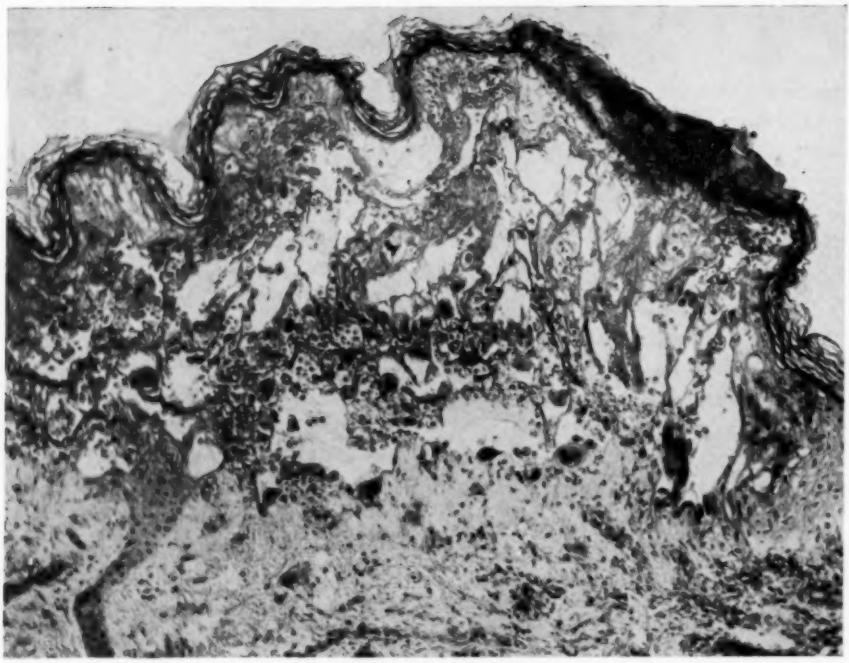

Fig. 1.—Photomicrograph of skin. One of the vesicular lesions showing the multinuclear cells and intranuclear inclusions. (Hematoxylin and eosin; ×140.)

Fig. 2.—Heart. The left atrial endocardium, the mitral valve, the chordae tendineae and the ventricular endocardium are thickened. There is hypertrophy of the left ventricle.

the vesicles are usually much better developed. There were a few petechial hemorrhages on the serosal surfaces of all the body cavities, and a slight increase in fluid in all the cavities. The lymph nodes, both peripheral and visceral, were very small, as was the thymus, the latter weighing only 9 grams, compared to a normal of 35 grams. The thymus showed inclusion bodies within Hassall's corpuseles, within various other cells, including lymphocytes. The heart, which was interesting in view of the history suggestive of rheumatic fever, did show gross changes which I think we can be certain were those of rheumatic fever. The heart weighed 165 grams as compared with the normal of 100 grams. It was flabby; there was moderate dilatation of all the chambers, and the endocardium of the left atrium and ventricle was thickened. There was a typical deformity of the mitral valve, which must have been incompetent and functionally may also have been stenotic (Fig. 2).

DR. JANEWAY.—Were there no vegetations?

DR. CHEATHAM.—No. There was a definite myocarditis with inflammatory infiltrate of a relatively mild nature in a few places, suggesting Aschoff bodies, though there are no clear-cut ones. (Fig. 3). The lungs were extremely interesting. These lungs maintained their shape; they were firm, suberepitant, and weighed twice the normal weight. There were numerous hemorrhages on the pleural surface, some with a lobular distribution, others petechial in character. There were, in addition, a few small vesicles on the pleural surface. The cut surface was congested and consolidated in areas 2 to 3 cm. in diameter. Inclusion bodies could be seen in the bronchial epithelium, fibroblasts, and other cells, and there was a diffuse mononuclear cellular infiltration. A few hyaline membranes were formed. The spleen was normal in size. Along the anterior edge and on the cut surface there were numerous verrucous and vesicular lesions. On the cut surface there were focal areas of necrosis measuring 1 to 2 cm. in diameter (Fig. 4). The spleen had numerous inclusion bodies within the sinusoidal lining cells. The liver, grossly, had small focal areas of necrosis which microscopically were hemorrhagic areas, with occasional inclusion bodies in the liver cells, endothelial cells, and fibroblasts (Fig. 5). The histologic changes in the ovary supported the clinical idea that the hemorrhage and shock were the direct result of the varicella infection. About the follicles there were extreme congestion and hemorrhage and these changes were consistently related to the presence of intranuclear inclusion bodies (Figs. 6 and 7).

At the time of autopsy we collected vesicle fluid, blood, and organ samples for tissue culture studies. With Dr. Thomas H. Weller's help we were able to isolate a virus which we believe to be that of varicella. The tissue culture methods are not such that one can quantitate the amount of virus, but there was a definite impression that there was a tremendous amount of virus in the blood. This agent failed to produce disease in suckling mice, and has been identified as that of varicella by complement fixation with known varicella antigen. The serum obtained from this child at autopsy failed to reveal any definite complement fixing antibodies against a

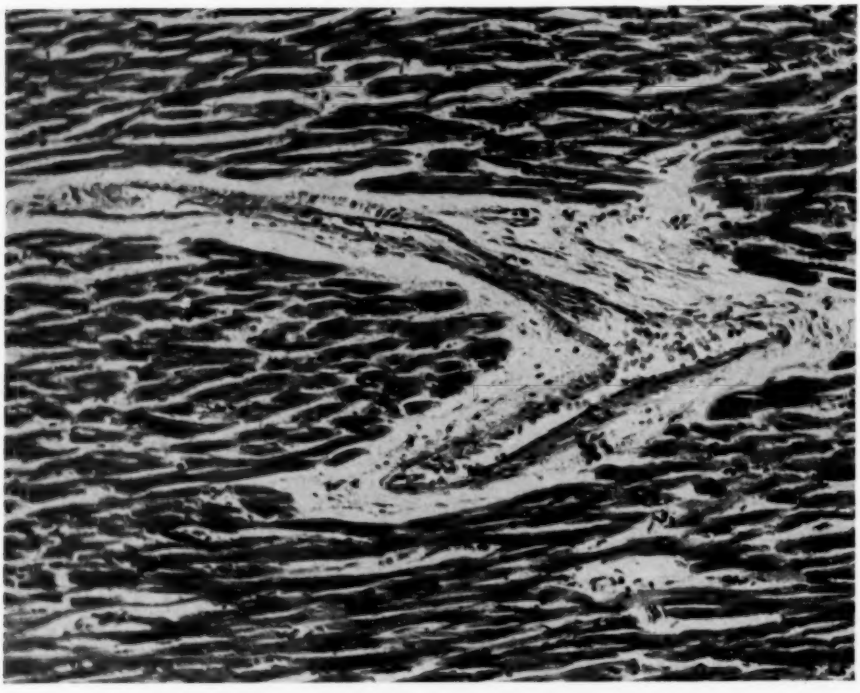

Fig. 3.—Photomicrograph of heart. Minimal fibrosis and a few mononuclear cells are found in the perivascular space. (Hematoxylin and eosin; ×190.)

Fig. 4.—Spleen. Numerous foci of necrosis are present surrounded by areas of congestion.

Fig. 5.

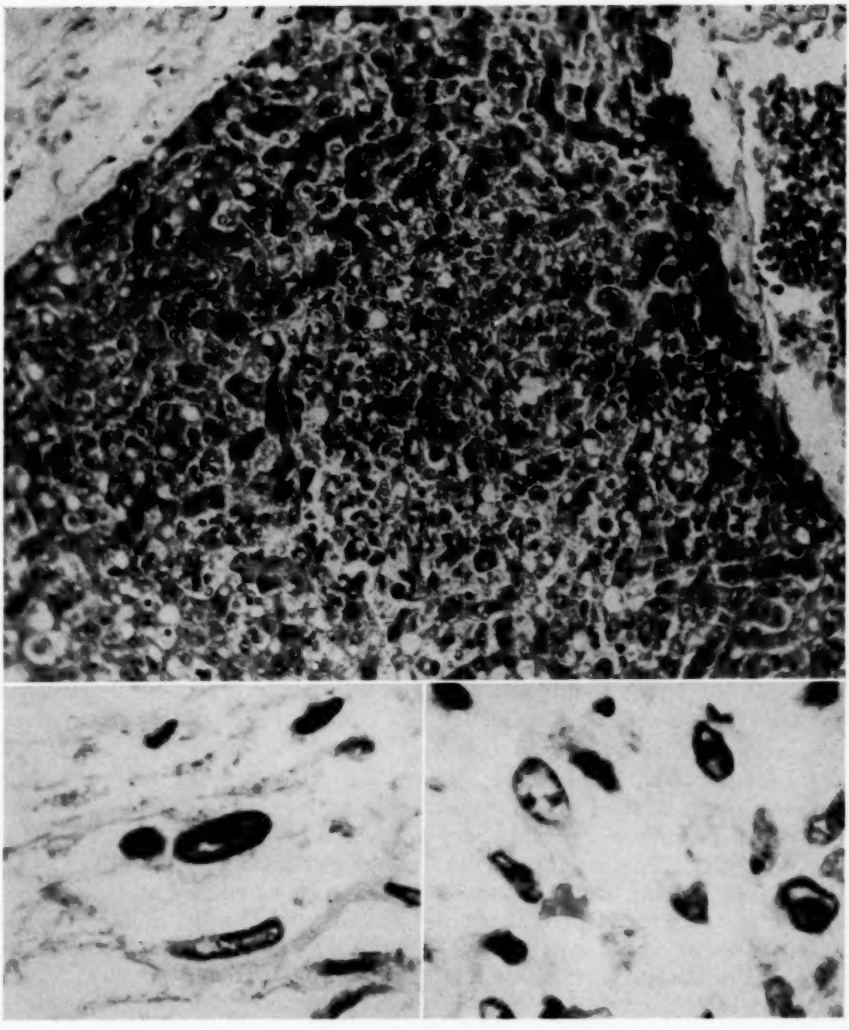

Fig. 6. Fig. 7.

Fig. 5.—Photomicrograph of liver. A focus of necrosis is present which is sharply outlined. (Hematoxylin and eosin; ×250.)

Figs. 6 and 7.—Photomicrographs of ovary. Inclusion bodies are present in the ovarian stroma. (Toluidine blue eosin; ×1,070.)

herpes zoster antigen. Dr. David Gitlin ran some studies on the serum protein and just how far we can interpret these I am not sure, because of the fact that the child did get so much blood, but that, together with many other factors, would lead you to believe that the child would not have agammaglobulinemia.

DR. BENEDICT F. MASSELL.—I would like to ask Dr. Kass a question. First, assuming cortisone therapy in rheumatic fever is efficacious at a 300 mg. dosage daily, should that therapy be given at home? Second, are there statistics on whether patients with fulminating varicella always have some underlying disease, as leukemia, or have been given hormones which lower resistance?

DR. KASS.—Just to answer a few of the questions that have arisen, probably the most critical is the problem of management, which Dr. Eley brought up. I wish I did have the answer. In managing a case like this, we have two problems. One is the management of acute adrenal insufficiency that would follow if one stopped cortisone, and which could not be made up rapidly enough by giving ACTH. The second problem is the management of the increased susceptibility to infection that stems from the use of cortisone. One might present the thought that corticosterone might be a way to get around this problem. Corticosterone, or one of the salt-active derivatives of cortisone, would help the adrenal insufficiency and not greatly add to the diminished susceptibility to infection. This is a purely speculative thing; we have very little data to support it, but it is based on the following considerations. The predominant steroids in the adrenal secretion of every animal that has so far been studied, including man, consist either of hydrocortisone, compound F, or corticosterone, compound B, or mixtures of these two. Corticosterone, which we have tested rather extensively, has very little adverse effect on resistance to infection. In the same dosage level as used in the case of cortisone and hydrocortisone, it does not diminish antibody production, and it doesn't increase susceptibility to induced infection.

DR. MASSELL.—Does it supress an inflammatory reaction?

DR. KASS.—It does not, in the same dosages, so far as we can tell. I have no doubt at all that in very large doses it will have some effect of this sort. Furthermore, corticosterone is very good replacement therapy in Addison's disease and is effective in the maintenance of mineral, carbohydrate, lipid, and protein metabolism. It has a stronger salt-retaining effect than hydrocortisone.

The whole concept of "covering with antibiotics" seems to be a nebulous one at best, and the whole idea of prophylaxis under conditions other than those aimed at a specific organism is open to question. Experimentally, it can be shown that nonbactericidal antibiotics which, in essence, means the broad-spectrum group, have very little "covering effect" in the presence of cortisone, simply because these drugs are not effective without the host-defensive mechanisms that are depressed by cortisone. Even with penicillin there is some depression of effect. Yet

penicillin is partially effective for two reasons: penicillin will kill susceptible bacteria, regardless of the host response; and, penicillin is a unique drug, in that we can administer safely doses many times larger than the usual minimal effective dose. This is not true of other drugs we know. Most of the infections that we see following the administration of cortisone are penicillin-resistant types, since these patients have all been "covered," so the kinds of problems we run into are not handled by penicillin.

To come back to Dr. Massell's point, I did not intend to imply that 300 mg. of cortisone ought to be given outside the hospital. As I say, 100 mg. and probably 200 mg. seem to be no more effective than salicylates in suppressing rheumatic fever activities in controlled studies, and we are just going to have to wait for further controlled observations to find out whether 300 mg. is more effective than 200 or 100 mg. At this moment, I am frankly unconvinced that 300 will be more effective. I hope it will be more effective, but want to see the data. I think the other important aspect to this is that we are dealing with such a potent agent that the dictum *primum non nocere* really requires more emphasis than we have given it. The old problem of weighing the harm against the good becomes critical. Seeing an occasional spectacular result may not suffice as evidence for broadening the use of these agents.

[This case is also reported by Drs. W. J. Cheatham, T. H. Weller, T. F. Dolan, Jr., and J. C. Dower, in the *American Journal of Pathology*, vol. 32, page 1015, 1956.]

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CLASSIFICATION AND ETIOLOGICAL FACTORS IN MENTAL RETARDATION

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BECAUSE of the limitations of time, it is the purpose of this presentation to summarize briefly the more important pathological cerebral mechanisms and clinical syndromes that are basic to the problem of mental retardation. While confining ourselves at this time to what may be considered the "organic" determinants of intellectual inadequacy, we do not intend to minimize the importance of psychogenic or environmental factors in the over-all problem. These, we hope, will be covered by the other contributions to this institute.

Well over a hundred different etiologies, diseases, and syndromes have been described in which mental retardation represents a more or less important symptom. Most of these, however, are extremely rare, some to the point of being considered medical curiosities. About 20 per cent are encountered with sufficient frequency to have practical importance, and it is this group to which we intend to confine our attention at this time.

They can be etiologically classified, most effectively, into three large groups, depending on the period of life during which their causative mechanisms are established: (1) the prenatal; (2) the natal and paranatal; and (3) the postnatal. The data relative to incidence of the various conditions that will be offered refer to our experience with over 2,500 admissions to the Southbury Training School for Mentally Retarded, in Connecticut. Like any other institutional statistics, these cannot be considered as random selections and therefore indicative of the over-all situation in the country. Obviously, children are committed to institutions not only because they are mentally retarded, but also because of associated sociological and psychogenic factors not related to the etiology of the mental retardation. It is also clear that institutions, as a rule, contain a much greater proportion of the more serious retardates than will be found in the community as a whole. Thus, various surveys in this country and abroad have indicated that approximately 75 per cent of the mentally retarded are in the minimal or high-grade category, 20 per cent in the moderately retarded or middle-grade category, and about 5 per cent in the severely affected or

From the Southbury Training School.

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low-grade category. The proportions of these different categories in the Southbury admissions, however, are in the order of 40 per cent high grade, 30 per cent middle grade, and 30 per cent low grade. It is to be expected that those conditions, genetic or otherwise, that result in the more extensive cerebral abnormalities will tend to be more numerous and important in our institutional population than will the less devastating etiologies.

PRENATAL MECHANISMS

Hereditary Factors.—The importance of genetics in the causation of mental retardation has been variously estimated to cover from 5 to 75 per cent of the problem. This may be because of the failure to differentiate the two distinct groups which are included. In the first group, to which the term "familial" or "subcultural" retardation is applied, the genetic determinants might properly be called "physiological," in that they represent a part of the genetic pool which determines the hereditary transmissions of normal intelligence. Intellectually inferior individuals in this category inherit from their parents those genes, undoubtedly multiple in nature, which determine their position in the lowest levels of the normal distribution curve of intelligence. These represent our intellectually marginal population whose social adequacy will be closely related to the nature and complexity of the society in which they live at the moment. Their problem is basically sociological, and their numerical magnitude will depend on the efforts of society to meet their special needs. There are no reliable data to indicate their extent in the general community at any one time. However, some concept of the importance of this group is indicated by our Southbury statistics in which they represented approximately 40 per cent of our total inmate population covering over 2,500 admissions. This so-called "familial" group, as might be expected, has the most promising prognosis. Of the more than 700 individuals discharged from Southbury during the last ten years, either to their own homes, gainfully employed, or to working homes, by far the greatest proportion (70 to 80 per cent) belonged to this group. Similarly, of those being managed in the community through local facilities, such as special classes and guidance clinics, the best results, by far, have been in this familial category.

The second group in our hereditary category represent an entirely different mechanism. The genetic factors involved in these patients are truly pathological in that they determine abnormal cerebral, structural, and metabolic manifestations. These conditions, which are fortunately few in number although diverse in nature, are due, as a rule, to single, mutant genes. They may be discussed most conveniently from four aspects. First are a number of diseases which have been called "inborn errors of metabolism." The responsible genes determine either the absence of, or the interference with, a specific enzymatic activity. They are represented in each of the various metabolic processes, involving proteins, carbohydrates, and lipids. Of the more important conditions represented here are:

1. Phenylpyruvic disease, which involves a defect in protein metabolism,

specifically, the absence of the enzyme system which determines the metabolism of phenylalanine.

2. Galactosemia, involving a defect in carbohydrate metabolism and specifically affecting the metabolism of galactose.

3. Glycogenosis, also involving carbohydrates, specifically affecting the metabolism of glycogen or animal starch.

4. The Tay-Sachs' group of cerebral lipoidoses in which the intracellular lipid metabolism of the brain cells is abnormal.

5. The white matter or myelin degenerations, also called the cerebral scleroses, a lipoidal defect.

6. Gargoylism, a disease of a complex nature probably involving more than one metabolic system.

The importance of this group of metabolic disorders lies not in their frequency as compared to other causative mechanisms, since they are rare, or basically in the eugenic implications of their recognition, important as this is. It lies in the relatively recent advances in our understanding of the mechanisms by which the respective metabolic disorder injures the brain or interferes with its growth and function, and the development of methods to circumvent this injurious activity. It thus represents a new and hopeful approach to the medical management of genetic disorders, namely, the prevention of the clinical expression of the genetic factor. So far, two of these have yielded or seem to be yielding to this technique, namely, galactosemia and phenylpyruvic disease.

A second group of genetically determined conditions have in common the fact that in addition to the cerebral defect, the disorder also results in a maldevelopment of the skull, by which the condition can be recognized and properly categorized. These include primary microcephaly, craniostenosis or premature cranial suture closure, and hypertelorism. It should be stressed that not all children with these skull defects show cerebral abnormalities. Conversely, in practically all of these cranial anomalies there is no obligate cause-and-effect relationship between the distorted cranial shape and the cerebral dysfunction, if present. Thus, surgical procedures designed to prevent or ameliorate the cranial anomaly, as for instance in the craniostenoses, may have little or no effect on the underlying cerebral defect, and prognosis should be guarded.

A third group of genetically determined conditions have in common a cellular dysplasia that may include many organs of the body in addition to the brain. Three such conditions are recognizable, but with so many similarities and overlapping of clinical features and familial genetic expressions that a unitary genetic mechanism is suggested. These clinical syndromes, commonly called the congenital ectodermoses, include tuberous sclerosis, neurofibromatosis, and cerebral angiomatosis. One of the most striking features of this group is the almost unbelievable variability of expression of the responsible gene or genes. A parent carrying the genetic factor involved may have, as the only clinical expression, a small skin lesion of no practical importance to his social status. Yet, his offspring may be completely devastated by the cerebral dysplasia and other organ defects. When we have learned which factors, genetic or otherwise, are responsible for such a variability in the clinical expression

of an inherited condition, we may have another key to the possible bypassing of undesirable genetic traits; this would be in addition to that applicable to the metabolic disorders previously mentioned.

Finally, in our genetic survey, we have a group of conditions, probably variable in nature, and more disturbing to us than those mentioned above, since they cannot be recognized as yet as being genetically determined except through the birth of a similarly involved sibling. In other words, unlike the above-mentioned inherited conditions, there are no recognizable associated disorders, and the only presenting symptom is the intellectual defect, which is nonspecific. The dilemma which such a condition presents to the medical counselor is at the present time insurmountable. Fortunately, these conditions making up this last group are relatively rare, and such a category was diagnosed in only 1 per cent of our Southbury admissions.

The total incidence of inherited conditions due to pathological or mutant genes (not including mongolism which may have a genetic component in its etiology) represented about 5 per cent of our total admissions.

Other prenatal conditions not definitely genetically determined and mentioned above have an incidence of about 10 per cent in our series. These include:

1. Prenatal infections, of which we recognize at least three; namely, congenital toxoplasmosis, maternal rubella, and congenital syphilis. Cytomegalic inclusion disease may represent a fourth, but its relationship to the mental retardation problem has yet to be established.

2. Kernicterus, a cause of mental retardation, is a disease of the neonatal period resulting from high levels of bilirubin in the infant's blood due to various mechanisms. While rightfully not belonging in the prenatal category, it is placed here, since the most common clinical condition responsible for its development is erythroblastosis fetalis due to maternal Rh immunization. An appreciation of the importance of the hyperbilirubinemia as the etiological mechanism, and the development of techniques to combat it (exchange transfusions) have reduced the incidence of this condition almost to the vanishing point in certain clinics.

3. Endocrine disorders are quite common among the mentally retarded. Basic cerebral injuries of one type or another may involve the nervous connections of the pituitary gland, and various factors affecting the brain at certain periods of prenatal life may conceivably also adversely affect other endocrine glands. However, the only hormone for which a reasonably acceptable cause-and-effect relationship with mental retardation can be established at the present time is the thyroid. It is also becoming more apparent that the cerebral abnormality resulting from complete absence of this hormone may well be established at the time of birth or quite soon thereafter in many of the cases. This probably explains the relatively poor prognosis encountered even in cretins treated within the first month of life.

4. Finally among the recognizable conditions prenatally determined, we come to mongolism, which was established as a syndrome almost ninety years ago and whose complete etiological story remains to be told. While

advanced maternal age is accepted by all as one factor, and implies an environmental causative mechanism, there is also strong evidence to implicate some type of genetic mechanism as well. As yet, the nature and mechanics of expression of this genetic factor have not been established. The incidence of mongolism in our Southbury data is about eight per cent.

A total of about 90 per cent of our admissions were classified as either genetic or otherwise prenatally determined. If we add up the conditions already discussed, we are left with a prenatally determined group of unknown etiology representing about 35 per cent of the total. This is a substantial number that bears strong witness to the limited nature of our knowledge of prenatal abnormalities and to the great need for continued research in this area. Studies of pregnancies resulting in abnormal children, including the mentally retarded, have shown a significant incidence of such conditions as early maternal bleeding, suggesting imperfect placental attachments, toxemias of pregnancies, including eclampsia, and prematurity. The nature and importance of the role these abnormal conditions play are still being evaluated.

CEREBRAL INJURY DUE TO FACTORS ASSOCIATED WITH THE BIRTH PROCESS

In our Southbury survey, mental retardation due to cerebral birth injury, neonatal asphyxia, or other mechanisms associated with the process of birth was diagnosed in about 3 per cent of the admissions. A high incidence of associated neurological abnormalities, like cerebral palsy and convulsive disorders, was found in this group.

POSTNATAL CONDITIONS

Approximately 6 per cent of our admissions could be related to postnatal conditions of various kinds. The most common included inflammations of the central nervous system, like meningitis and encephalitis. The next most common cause was cerebral trauma as a result of various accidents in infancy. Occasional mention is made of accidental poisoning with lead, carbon monoxide, and coal-tar derivatives. It was also somewhat disconcerting to find at least two cases resulting from vaccination against pertussis and one after smallpox vaccination.

To summarize this brief survey of etiologies, we may say that the causes and mechanisms involved in the problem of mental retardation are many and greatly varied. In our Southbury survey, approximately 40 per cent represented the familial group, or lower end of the normal distribution curve for intelligence. About 5 per cent were due to specific pathological mutant genes, and 10 per cent were classifiable, prenatally determined, nongenetic, acquired conditions. Another 35 per cent were also prenatally determined, but were unclassifiable and of unknown etiology. Only 10 per cent represented the group injured at birth or in the early postnatal years.

ROLE OF PHYSICIAN IN MAINTAINING CONTINUITY OF CARE AND GUIDANCE

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A PHYSICIAN who has the opportunity to work with retarded children and their parents sees many children after they have already visited a great many doctors. The help these parents and children require is something quite different from that needed by the average patient. The physician who stops with making the diagnosis of retardation in a child has missed an opportunity to accomplish something of value to the patient and of satisfaction to himself. It is not difficult to make a diagnosis on a retarded child with the aid, if necessary, of laboratory work, x-rays, and perhaps a consultation or two. Then, even though the findings are communicated to the parents in such a way that they accept the diagnosis and are not angry with the doctor, there is still much more that the physician has to contribute.

No physician would, for a moment, examine a child suspected of having rheumatic fever and, when the examination was complete and the diagnosis established, simply tell the parent that the child had rheumatic fever and let them go on their way. He would follow the rheumatic fever child for the duration of his disease and keep him under close surveillance for some years afterward. He would have no question about doing this and yet, with the retarded child, an altogether different approach is used. The retarded child and his parents have just as much need for the physician's continuing interest and follow-up as the child with rheumatic fever.

Let us consider some of the things that the physician might do that would be helpful to the parents and to the child. If the diagnosis of retardation is made at birth or shortly thereafter, as is sometimes the case in mongolism, the physician has a very important role to play. He would not recommend that these children be institutionalized immediately except perhaps in extreme cases where the mother, for physical or psychologic reasons, might be unable to care for the infant. Even then, there often are better places for infants than institutions. This situation is rare and the physician should continue to help the mother raise the child in the way best for the child. A mongoloid child who is seriously retarded has some potential; if his needs are met during the first few years of life he will be able to better utilize the limited potential he has.

What do these children need during their first few years? For one thing they need the same sort of relationship

From the Child Health Center and Clinic for Child Study, University of Washington.
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with the mother as that needed by any normal child. So often, because the child is different, the mother feels different about him and treats him differently. Mothers often say they just do not know how to handle such a child. These mothers need to be seen periodically just like the mothers of normal children. They need to have their questions answered, to be told about feeding, development, and all the points with which any unsure mother needs help.

The physician can call on other persons for help. He may find the public health nurse useful in demonstrating physical care of the infant, discussing feeding problems, giving suggestions about appropriate toys, or any of the things that a trained person can do who has the time to talk in a relaxed manner with the mother in her own home and to make on-the-spot suggestions. Often a good public health nurse can do a tremendous amount of good just by letting the mother talk and offering understanding and sympathy.

Again, a mother may have a hard time accepting her child's retardation and may be emotionally upset. Sometimes the father and mother are at odds over what to do about the child and are not of any mutual support. The physician, by talking to the father and helping him to accept the situation and be more supportive to the mother, can contribute much to lessening of family tension. If the doctor feels that the situation needs more time than he can give, the family can be referred to a social agency, such as Family Society. If there is no family agency in the community, then perhaps the social worker in the children's division of the welfare department might help. The children's worker in the welfare department can be a most interested and helpful person in many ways.

The important thing is that the physician keep aware of the needs of the retarded child and his parents and know what resource persons his community has, in order to make effective use of them. He must not, however, turn the family over to them and step out of the case, but should continue to play an active part, integrating and coordinating the work of different people and agencies. He must know what the other persons are doing and when an agency has fulfilled a need and another type of help is indicated.

In addition one should follow closely the child's physical condition, because of his susceptibility to illness. Many retarded children have dental, nutritional, orthopedic, or speech problems, and the like. It is important that defects be corrected and the child be in as good physical condition as possible. A child who is already limited mentally can have his functional ability much further reduced by physical problems. Conversely, by correcting physical defects one can often increase the child's total functional capacity.

The retarded infant needs to be loved and cared for, just as any other baby does. If the mother has difficulty accepting the child or feels that he is different and therefore does not need affection, the physician can help her with this adjustment. A few weeks ago I saw a mongoloid girl 15 months of age. This child had remained in

the hospital since birth. It was a good hospital and the child had had good physical care and probably a little more attention and affection than is usual in most hospitals. The mother had visited her two or three times a week. The child was in good physical condition and had had a minimum of infections during her life. However, the parents were concerned because they felt this child was more seriously retarded than most mongoloids. They told me that the child never smiled nor seemed happy and did not appear to know the mother or the nurses. It became obvious as we studied the child that she was not really more retarded than the usual mongoloid child—in fact the child tested somwhat higher than average for this group—but, having been raised in such an unstimulating atmosphere as even the best hospital can offer, the child was simply showing the apparent retardation due to lack of stimulation. This is a situation a physician should try to prevent. There was, in this case, some reason for the mother's not taking the child home with her. She had a number of other children and had had, in the past, a mental breakdown. She did not want to take the child home and was able to afford private care. A much better solution would have been to place this child in a foster home where she could have had the love and warmth from one person that is so important for any baby's emotional growth.

If the physician's first contact comes when the child is of preschool age, or as the child he has followed reaches this age, he must be aware of the changing needs of child and parent. With the retarded child, just as with the normal one in preschool years, experiences outside the home and with other children become important. It is also important for the mother of the retarded child to get some time away from her child. If the child is retarded to such a degree that he is unacceptable in a normal nursery school, it may be possible for the mother to get together with other mothers of retarded children and organize a special nursery school.

An important resource in such an effort would be the local association of parents of retarded children. Such a nursery school might already be in operation or perhaps mothers in that group could establish one. This, of course, is not the only use of the parents' organization but I shall not at this time go into detail concerning the many ways this organization can be of help to parents. Let me say, however, that getting the parents of patients in contact with the association does not mean that the physician's continued interest and coordinating efforts are less needed.

The physician will sometimes find that his chief task is to convince the parents that a child is not defective. Many children have been referred to our clinic by physicians, teachers, and social agencies where there was no doubt in the minds of the parents or referring person that the children were mentally retarded. A thorough study, including psychologic and psychiatric examination, has revealed that the children were not defective at all, but emotionally disturbed. In many cases the condition could be reversed but, in order to accomplish this, it was necessary that an active psychotherapy program be started immediately. Again, the physician is in

the best position to cause such an evaluation or re-evaluation to be made. Recently a 7-year-old boy who illustrates this type of problem was referred to our clinic. The boy was attending the School for Retarded Children in his local area and, inasmuch as he had never been thoroughly studied, was sent for evaluation. There was no question in the minds of the personnel of the school or in that of the mother that he was retarded. The mother planned to place him in the state training school for retarded children as soon as he could be accepted. Our diagnostic procedures revealed nothing medically to indicate a basis for retardation. The boy's I.Q. score was only in the sixties but it was obvious that his fearfulness and tremendous anxiety on being separated from his mother were large factors in his poor performance. The child had had a traumatic life. At 2 years of age a sibling had been born. Shortly after that, his father died. The mother moved, while being emotionally upset herself, into her grandparents' home, where the child was cared for by a doting great-grandmother. The mother felt that her grandmother spoiled him too much; so after a few months she moved out. The emotional trauma, in addition to being raised by a rather unhappy, rigid mother, contributed to the boy's condition. He needed psychiatric help and not placement in the state institution for retarded children. Unfortunately, there is a sizable number of children who are thought to be retarded but who are really ones with emotional problems. In this case we were able to get the school guidance department, the school principal, and the teacher, as well as the social worker from the local child guidance clinic, together and plan a program to help this boy. The coordination was done by our clinic. Many children, however, are not going to be seen in a special clinic for retarded children. The physician can meet with school and guidance people and help plan an effective program.

Schoolteachers and administrators are generally interested and cooperative concerning the problems of the retarded child and can do a lot to help. Usually they need and appreciate the interest and guidance of a physician. Most feel uncertain about the physical aspects of the case and work more effectively as a member of a team focused on helping the child rather than alone, having the entire responsibility left to them.

There are also some children who are just slow in maturing and need only time, together with the parents' patience and understanding, to function in a more adequate manner. Here again the physician is in the best position to help the parents carry out such a program of waiting. The resources one utilizes depend not only on the needs of the child, but also on those available in the community. Some areas are much more fortunate than others. There are always public health nurses, at least a child welfare worker connected with the local welfare department, and, of course, people within the school system who can and will work effectively with the physician. Of course, personalities must always be considered. Some people just naturally work well with children who have mental problems and others do not. It is up to the physician whenever possible to determine what individual will best meet the needs of his patient.

SUMMARY

The physician must make the parent realize that his interest in the child is a continuous process. Unfortunately the impression so often given is that when the diagnosis has been made the physician is interested in seeing the child again only if he is ill. The physician must think of his role in relation to the retarded child as a broad one. Advice, support, understanding, direction to other people and other agencies and resources that can be of help to the patient—these are things that someone must supply, and the physician is the logical person to offer them. He is well equipped to give advice, support, and understanding to the patient and the parents and to direct them to other workers, agencies, and resources that can be of help to them.

A remarkable instance of a diseased ovarium, in a child of about eleven years of age, under the care of Doctor Aspinwall at Roxbury, who, after attending six weeks, requested that Doctor John Warren of Boston might meet him in consultation. Upon their examination of the abdomen, it was found to be greatly distended with some fluid; but the hypogastric region appeared to contain a hard, unequal, schirrus-like substance, which was more or less perceptible in size and extent, according to the quantity of fluid contained in the abdomen, which at times was so great, as to obliterate the tumor, and could be felt only by considerable compression. It was agreed to make an incision immediately upon the tumor; but no disease external to the peritoneum was found. The operation of paracentesis was then performed, and several gallons of a viscid fluid drawn off. Six days after, the child died. The water had again collected, in a greater quantity than before. The viscera in general were diseased. The omentum adherred to the surface of the intestines. The fallopian tubes and ureters were enlarged much beyond their natural size; and the left ovarium, extending from the left towards the right side six or seven inches, exhibited numberless hydatids filled with gelatinous matter. This ovarium, independent of any other viscus, weighed four pounds.

From an Inaugural Dissertation on the Dropsy, by William Dix, Worcester, Massachusetts, 1795.

RESEARCH IN THE FIELD OF MENTAL RETARDATION

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WHAT I planned to discuss at this time were some of the promising avenues of research which are being investigated in various parts of the country. Before I do that, I would like to say a word about the general problem of research in a field such as that of mental retardation. I am going to confine my discussion to the medical aspects of the problem; however, I think it is well to recognize that research is not purely a medical problem alone. There is just as much need and there is probably just as much if not more, being done at the present time in such fields as education, training, community management, and institutional care as there is in the purely medical aspects. The field of research in mental retardation is complicated by the fact that we are dealing basically with a symptom, and mental retardation is essentially a symptom of a wide variety of clinical conditions and etiologies. Each one of these individual conditions is relatively infrequent, with some exceptions. Even if we learned the pathogenesis of any single condition previously unknown, we would be barely scratching the surface of the over-all problem of mental retardation. To study any one of the problems is extremely laborious, and probably would take as much time and ingenuity to solve as it did for a disease like polio where one solution might answer the entire problem. In mental retardation we can solve only a very small segment at a time. This explains, in part, the discontent of parents and other lay people with the apparently slow progress in the field of research, even though there is a great deal being done.

The other problem I should mention is the fact that research in the field of mental retardation is dependent to a great extent on what we may call fundamental, or basic, research; that is, research in a wide variety of the fundamental sciences, like embryology, virology, genetics, etc. To determine which of these avenues has application to the field of mental retardation is sometimes exceedingly difficult and requires an extraordinary degree of imagination. To give one example of this, I am sure that the person working with the Rh factor and studying how red cell typing differs among people had not the slightest idea that this one piece of research might at least explain what is essentially an important aspect in the field of mental retardation. It took many devious steps before it went from the purely scientific approach in the laboratory, through the various clinical fields, to its direct application to erythroblastosis, and finally ended up as the etiology in a specific group of brain-injured children. One can mention

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many such examples; the development of the technique of paper chromatography is only just beginning to appear as a research tool in the field of mental retardation. It was designed probably for other purposes. We are greatly dependent on various other disciplines to develop for us tools and techniques that we can apply to the field of the mentally retarded. These tools and techniques are so specialized in themselves that few working in the clinical field of mental retardation could, alone, develop techniques or even apply such techniques without a good deal of specialized study.

There are a number of very interesting avenues at the present time which I am sure will have definite application to our problem.

1. One that is being pursued in a number of institutions and universities in the country, and which may have application to the field of mental retardation, is the search for metabolic disorders that may be responsible for abnormalities in various patients, not necessarily the mentally retarded. At the present time this is confined, more or less, to screening procedures. In various laboratories, paper or column chromatography screening of urine and blood of large numbers of mentally retarded inmates of various institutions is being used to identify specific abnormal metabolites. This might give leads to determine which specific cases should be studied more closely. This is being applied not only in the field of protein metabolism but also in searching for abnormal carbohydrates in the urine and blood.

2. I attended a symposium some months ago in Cincinnati, which was an exceedingly exciting experience. This included a group of individuals whom my clinical friends and I rarely meet professionally. It was a meeting of experimental embryologists and experimental teratologists interested in how a fetus is influenced by environmental factors. They were working with chicken eggs and fetuses of guinea pigs and rats and rabbits, etc. As I pointed out previously, 90 per cent of our whole problem group, at least in our institutional population, is prenatally determined. If we eliminate the 40 per cent which are due to normal inferior genes, we still have 50 per cent of our problem due to prenatal factors acting on the fetus in various periods of fetal life. These people were studying the stages of fetal development at which specific abnormalities can occur and the nature of the specific agents that affect the fetus. An interesting point was the wide variety of agents that may be toxic at different fetal periods, and how selectively active these were, depending on the time of application. Thus according to certain experiments, if the fetus is injured or is exposed to specific factors on the seventh day, nothing happens; but on the eighth day it might be seriously affected; yet, if it is exposed on the thirteenth day, it is spared. These experiments cannot be readily translated in terms of human experience at this time. But a knowledge of the nature of these noxious agents and how they may be influencing the fetus is extraordinarily important from our point of view. Evidence was also presented to indicate the importance of genetic factors in determining the degree of reaction by a fetus to specific noxious agents. In one strain of animals resistance to the injurious effects was high; in another strain practically

all fetuses were affected. The implications of these studies for diseases which we now accept as being genetically determined are obvious. That the genetic status may represent only one aspect in the etiology of some of these conditions and that additional environmental factors may also be involved suggest exciting possibilities of prevention in a field heretofore considered hopeless except for sterilizing procedures. Other implications are also raised. A disease like tuberous sclerosis is readily accepted as a genetically determined condition, and so explained. However, how can one explain the observation that in the same family in which the condition appears one child may show complete neurological devastation as a result of the disease, yet a parent or another sibling may have only an insignificant skin lesion as its only manifestation, or even no apparent symptoms? To explain this by the use of such terms as "penetrance" or "variable expressivity" is purely a semantic cloak to hide our lack of knowledge. Research along the lines cited above may well point the way to an effective clinical approach in some of our genetic diseases.

3. Another important field that is being investigated rather extensively is the study of pregnancies, both retrospective and prospective. Retrospective studies are those in which the mothers of a large group of mentally retarded children are questioned carefully as to the unusual events or conditions that may have taken place during the pregnancy, to determine whether some peculiar factor is common among these women. Obviously such experiments have many weaknesses, but they are not so extensive and laborious to carry out as prospective experiments, and have yielded much interesting and important material. The hazards of prematurity, and such disorders of pregnancy as eclampsia, the toxemias, and premature membrane ruptures have all been implicated as a result of this type of investigative procedure, and further information may be expected from many such studies now in progress. Prospective studies, or the careful investigation of many women of different ages and physical states throughout their pregnancy, using the available investigative procedures, and the subsequent correlation of the findings with any abnormalities found in the conceptus, represent a much more ambitious undertaking, since the numbers involved must be large. Only a few such studies are now in progress. Since the incidence of mongolism is so highly correlated with advanced maternal age, prospective pregnancy studies confined to women over 40 years of age should be most enlightening in attempting to elucidate possible environmental factors involved in the pathogenesis of this common disorder.

4. We have been aware that the mother can be immunized against the Rh factor carried by the fetus. There is some evidence to suggest that there may be other substances, possibly involving intermediate metabolites present in the fetus, which can also possibly immunize the mother and that the antibodies so produced might adversely affect the fetus. There are some studies going on along those lines.

5. We earlier mentioned the fact that we recognize only a very limited number of prenatal infections that injure the fetus: German measles, toxoplasmosis, syphilis, and cytomegalic

inclusion disease. There is rather extensive work going on looking for other viruses which might conceivably injure the fetus. The fetus is a rather well-protected parasite in the mother and probably a very limited number of noxious agents can by-pass the placenta.

6. The whole problem of prematurity is one that warrants and is receiving considerable attention. The incidence of mental retardation among premature children is very definitely higher than it is in the general population. We need to know two things: what happens in the premature infant that leads to brain damage; and, second, what bring about prematurity and how can it be prevented. The amount of work done in this field is quite extensive although no complete answer has come out yet.

7. We have always thought that the brain, or rather the individual neuron, once it is injured, never replaces itself, except for the glia cells. There has been some recent work with tissue culture techniques which seems to imply that under certain conditions it is possible to get ganglionic neuronal growth and replacement, at least in the test tube. The investigations have to do with defining the factors which stimulate this type of neuronal replacement and those factors which inhibit this type of neuronal growth. I am sure that that type of work will eventually have some application to our field.

Finally, we come to a type of research which you probably all are familiar with and which I call the "magic bullet" research. That is, regardless of cause of the mental retardation, is there a physiological substance or procedure that can conceivably influence intelligence so that it functions at a more effective level? We have lived through the introduction of many of these substances. You all remember glutamic acid, the vitamins, various hormones, and even surgical procedures that were supposed to have this ability. None have been significantly effective. At the present time, a good deal of the research is going on with the tranquilizing drugs, Serpasil, Thorazine, and others which are being developed, and there is no doubt that the drug companies are going to turn out many others along this line because it is very profitable. One does not mean to minimize this type of research; it is very essential and, if well done, is very worthy. Unfortunately, it is one of the most difficult types of research to do well, and yet it is one in which those least qualified to carry out research projects are engaging, with results that are complicating life for a good many of us who have to manage the mentally retarded.

I selected these topics which I felt were rather unusual and promising avenues in research. It is apparent that the more alert we who are dealing with the retarded are (and I am talking not only about those in institutions, but also about those who see the retarded in clinics and deal with the retarded in their offices) to what is being done in fields which seem rather foreign to us at this time, the more promising will be the possibility of translating this research into fields which may be definitely related to the problem of the mentally retarded.

PANEL DISCUSSION

MENTAL RETARDATION: TEAMWORK IN CASE FINDING, DIAGNOSIS, APPROACH TO PARENTS, AND GUIDANCE

Chairman

HARRY BAKWIN, M.D., Professor of Clinical Pediatrics, New York University, Bellevue Medical Center, New York City, N. Y.

Members of the Panel

HERMAN YANNET, M.D., Medical Director, Southbury Training School, State Institution for Mental Defectives, Southbury, Conn.; Assistant Clinical Professor, Department of Pediatrics, Yale University School of Medicine.

GEORGE TARJAN, M.D., Superintendent and Medical Director, Pacific State Hospital, Spadra, Calif.

D. S. STYLIANOU, PH.D., Director, National Association for Retarded Children; President, Orange County Parents Groups; Advisor, Orange County Board of Education, Santa Ana, Calif.

RICHARD KOCH, M.D., Assistant Professor of Pediatrics, University of Southern California School of Medicine; Medical Director, Mental Retardation Study Clinic, Childrens Hospital, Los Angeles, Calif.

DR. BAKWIN.—You have heard this morning from the doctors. I thought it might be interesting to start this afternoon by asking Dr. Stylianou what the reactions of the parents are toward the medical handling of the retarded child.

DR. STYLIANOU.—Up to now the reaction of the parent has not been as friendly or favorable as it might have been. Many parents have gone to their doctors for advice about their retarded child, and the doctor, either because of unfamiliarity with the subject or prejudice against mental retardation, has given the wrong answer and has hurt the parents to the point where they have become prejudiced and bitter. Recently a parent said to me: "We had a little mongoloid girl and, from the day the child came into the world, the doctor told us: 'It's a mongoloid, put it away.'" They went to another doctor and said: "What can you tell us?" The doctor answered: "Put the child away." Now, how can you expect the parents' attitude toward the doctor to be friendly? I wish there had been more parents present today to hear Dr. Yannet and the others. They have a philosophy toward this problem which, if it were adopted by others, would result in better feelings toward physicians.

From the Department of Pediatrics, Childrens Hospital, and the University of Southern California Medical School, Los Angeles, Calif.

Presented at an Institute on Mental Retardation, April, 1956, at Childrens Hospital, Los Angeles, Calif.

DR. BAKWIN.—Is it your feeling that the doctors are not sufficiently frank and outspoken?

DR. STYLIANOU.—Yes. They are not frank with parents and the parents lose confidence in them.

DR. BAKWIN.—Dr. Koch, would you like to defend the doctor?

DR. KOCH.—I have some specific thoughts about this problem. First, there is a lack of training in this field for the doctor. He is suddenly thrown into it and is expected to know all the answers. Pediatric residencies last two years. Think of the general practitioner, who takes one year of internship and who may devote one month of that one year to pediatrics. What a dearth of knowledge he must have in this field! Informing parents that their child is retarded is a very difficult and usually an unpleasant task. To do it properly requires time, and a pediatrician on a ten- to fifteen-minute schedule cannot possibly do justice to this problem. In our Study Clinic for Mental Retardation interviews often last as long as two hours. There is a lack of understanding by the physician of the serious family tensions in these parents. Occasionally the family is so distraught that they are not even listening to the words of the physician. What has registered is the fact that their child is retarded, and nothing else. These factors complicate the physician's problem and consequently the parents are often given the "brush-off" so to speak; then they wander from doctor to doctor without satisfaction. Finally there is a dearth of factual knowledge in this field available to the physician. Most of our ideas are personal impressions based on a few experiences. I know a physician who feels strongly that the mongoloid child should be placed immediately after birth; the reason is that he had a mother of a mongoloid child who committed suicide. Of course this mother might have committed suicide regardless of what her child was or was not; the mother who commits suicide because she has a mongoloid child must have had other problems too.

DR. BAKWIN.—Dr. Yannet, do you have something to say?

DR. YANNET.—One of the big problems in the relationship of the physician and the parent is that of communication: it is a problem of semantics. The physician will use the term "mental retardation" about a specific child, let us say one of a degree able to attend a special class, who later will probably be able to go out into the world and earn a living. He uses the same term "mental retardation" for a mongoloid child who is in the middle-grade category, whose future may allow him to earn a living but for whom there is a great deal of doubt as to his future possibilities. And finally he uses the same term when speaking of a child in the lowest level of mental capacity, one who will never be able to attend any kind of school. Many times the parent leaves the doctor's office with the diagnosis of mental retardation, but without the slightest conception of how the term applies to his own child. We have had, any number of times, a mother come with her child who is obviously retarded, to have him admitted to our institution. When we ask her what she believes the institution will be able to do for her child—let us say that the

child's eventual capacity might be expressed by an I.Q. of 15 or 20—she says: "Well I read a lot of books on the subject; my doctor told me this was a mentally retarded child, so I presumed that with the training and environment here at Southbury he'll be sent back to me and will be able to live in our home, because you have sent so many children back to the community." I know the doctor never said that in so many words, and there probably was not time for him to define terms which seem so obvious to the physician and are so novel to the parent. There is so much wishful thinking on the part of the parent that you never can get by with only a simple explanation. You have to go into great detail and make very certain that the parent understands the terms you are using.

DR. BAKWIN.—Dr. Tarjan, do you want to add something?

DR. TARJAN.—We have a rather serious problem when we speak about diagnosis and the question of conveying the meaning of it to the parents. The problem can only be solved by education aimed toward the professional person. So the prime responsibility lies upon those of us who have something to do with professional education. To say that your child is retarded has not much meaning, unless you translate it into very specific terms, applicable to this given child. Otherwise one puts the question of this child into a frame of reference that has nothing to do with this specific child, but has to do with the generality of an over-all term, namely, mental retardation. In medicine we make a diagnosis for two basic reasons; to classify certain cases and to determine certain types of treatment applicable to a given case. In mental retardation diagnosis is different because, at the time it is made, it has a long-term meaning, namely, a lifelong planning; therefore the diagnosis obviously implies also the necessity to convince the parents that this diagnosis is made for the specific purpose of planning for the future. This is the aspect in which we so often have problems. For instance, to the doctor referred to by Dr. Koch the diagnosis of mongolism immediately implied his modus operandi as to treatment, namely, institutionalization. The parents' modus operandi may be different from the one of the doctor and this will produce such a block between doctor and parents that not only is the method of treatment not conveyed, but even the understanding of the diagnosis itself is not realized. Telling parents frankly is often the block that makes further communication with the parents an impossibility. We hear generalizations in the case of mongoloid children, such as "institutionalize" or "do not institutionalize." Obviously neither of the two methods could be applicable to all mongoloid children. We need more understanding of what keeping a mongoloid child at home means to the child, the parents, the family; even more we must convey this understanding in such a fashion that the avenue of communication with the parents will not be blocked. Improvement in that respect will have to come from teaching professional people, since we cannot select in advance the future parents of the retarded child and train them to receive our professional expressions.

DR. STYLIANOU.—I think, Dr. Tarjan, that if the physician uses a little diplomacy and kindliness to give the parents the truth gradually, it will help them. To come right out and say, "Well he is retarded," is to be frank; but as you expressed it, Dr. Bakwin, there is a nice way of telling the parents. Some of the doctors make the diagnosis but they cannot go any further. I believe these doctors should familiarize themselves with parents' organizations, so as to be able to refer parents to them for help and assistance; meeting other parents with the same problems and sharing their experiences with them will be a great help. I hope, Dr. Koch, that your clinic will put a great deal of emphasis on the bedside manner in treating mental retardation, when you train interns.

DR. BAKWIN.—Many of the attitudes required are not necessary for mental retardation alone, but hold true in general for the care of the sick child.

DR. TARJAN.—I would like to emphasize one issue. Quite often the pediatrician meets the patient for whom no diagnosis has yet been made or where no diagnosis has been as yet accepted by the parents as valid. The parents' organization deals with parents who have accepted the diagnosis made of a retarded youngster in their family. It is my feeling that the medical profession can get enormous help and assistance from those organizations, even when there is still a minute doubt in the minds of the parents although none exists in the doctor's mind. The issue is to help the parents across this last line at a time when the doctor knows the diagnosis but the parents have not yet accepted it. Often they are not at all receptive to the suggestion of joining one of these organizations, because their stand is still: "There is nothing wrong with my child." The role of the parents' organization is an enormous one, helping the parents as well as us professionals, but there is an entirely different problem that confronts the pediatrician when he first meets mental retardation in the family, with unprepared parents.

DR. BAKWIN.—A very good point. Did you want to say something, Dr. Yannet?

DR. YANNET.—Just one word of caution: one must face the fact that for a parent to know her child is mentally retarded is a shock, no matter how you say it, and you can make just as much of a mistake by going overboard in an attempt to soften the blow as you can by being abrupt about it. It is well to point out that a great deal of the difficulties of communication with parents has come from the fear of hurting them by being too frank or abrupt. It is only fair to say that, with some exceptions, parents can take the most bitter medicine, take it and understand it; but they cannot take someone who is trying to let them down by simply being kind to them. If this is your only attitude, you may end up giving the parents an entirely wrong conception of what the problem is.

DR. BAKWIN.—Let us go on with some of the other points the parents criticize the doctors about. Would you like to go on, Dr. Stylianou?

DR. STYLIANOU.—Yes. The doctor wanting to please the parents will tell

them: "Some day your child is going to be a president." He builds high hopes in them, and this is just as dangerous as saying without any cause: "There is nothing that can be done for your child." When he hears this, the parent is not able to reconcile himself to a particular range of experience and refuses to send the child to any special class or school, but wants to force the child into a regular school.

DR. BAKWIN.—You mean the prognosis is not clearly stated to the parents. Would you like to discuss this, Dr. Yannet?

DR. YANNET.—There is hardly a field more difficult for the doctor to grasp than the one of prognosis. It is difficult and complicated, not only in expressing it to the parents, but in understanding it ourselves. Let us take a child of 3 or 4 years of age functioning on a 1½-year level, indicating a possible serious degree of retardation. You have made the diagnosis of mental retardation and the parent wants to know how much of a handicap this degree of retardation will be when the child gets to be 6, 8, 10, or 15 years of age. The point I want to make is how cautious you must be about being too direct in your prognosis. There are too many factors in the life history of a child which vitally affect the prognosis, but about which you have no idea when you first see the child. For example, what is going to be the reaction of the parents to the presence of this child at home over the years? This reaction will have a vital influence on how this child will utilize the capacity he has, and how he will adjust to the community. What type of personality will this child develop when he is 8, 10, 15, or 20 years of age? Is he going to be well related with people, easy to reach, adjusting well under various circumstances? You cannot make this prediction from looking at a 3- or even at a 5-year-old child. Finally, how can you know what the community facilities will be in five years, how adequate the special classes will be, and how competently the community is going to handle the problem? Without this information it is impossible to translate a degree of retardation into terms that will have practical meaning for the parents, and to express how much of a handicap the degree of retardation will eventually be. And it is impossible to generalize because you cannot use past experiences, since no two children are alike, no parents are alike, no communities are alike. One of the criticisms raised was the fact that the doctor does not present as complete a picture as possible. This is not only due to lack of experience, but no matter how much experience a doctor has there are certain types of information he cannot have at the time he sees the child for the first time. The doctor simply has to be patient and try to convince the parents that they cannot expect an accurate prognosis and that anyone who will give them one is not telling them what the case is and may be entirely wrong.

DR. KOCH.—Dr. Bakwin, you mentioned this morning that when you deal with the problem of a mongoloid infant you immediately tell the father. Then if the father wants you to talk with the mother you do so, or you talk with both of them together. It seems

to me that this can be a problem. Take the obstetrician who sees immediately at birth that the child is a mongoloid child. Do you feel the father is the person to talk to first, or maybe that one ought to talk to both parents together?

DR. BAKWIN.—First let me say that I think the obstetrician should do the telling because it is his patient, unless of course this is the second child in the family and you already know them and are not an outsider, so to speak. It has always seemed better to me to discuss it first with the father; after all, the mother has just been through an emotional experience and I see no reason not to discuss it first with the father. I don't know of any objection to speaking to both parents at the same time. Dr. Tarjan, what is your feeling?

DR. TARJAN.—I think Dr. Bakwin is completely correct. When the mother is still in the hospital the father is probably the right person to talk to first. However, later, when both parents are available, the pediatrician should try to speak to both at the same time if at all possible. This suggestion comes from my experience. Quite often when you speak to one parent, and I have heard their reaction in retrospect, one of the thoughts that keeps going through his mind, preventing his listening to the conversation, is: "How am I going to translate this to my wife; how can I tell her?"

DR. KOCH.—It seems to me that we are having better luck where both parents have been taken into confidence immediately. It does not seem to me that the male is any stronger than the female so far as taking unpleasant news is concerned.

DR. BAKWIN.—After the newborn period I do talk to both parents. During the war one of our former students had a mongoloid baby. The father was away in the Navy; his wife was in New York alone, had no relatives, and did not know many people. I did not tell her about her baby at first and finally decided to tell her when the baby was about 4 months old. It happened that at that time her husband was in town and he came with her. As she was dressing the baby in the examining room I talked with the father and it seemed to me that it took her a long time to dress that baby. She apparently understood there was something wrong. Dr. Yannet, in regard to prognosis, don't you think that from the behavior of the child and from the I.Q., you can get a general idea as to the range of potentialities of a child in later life, in a considerable proportion of cases?

DR. YANNET.—You can, but I don't think you can tell how much of a handicap this range of potentialities will be when he gets older.

DR. BAKWIN.—To tell a parent who asks you about a child's future development: "Well, I don't know, I can't say," does not seem quite fair. I do not think they expect a precise answer, but I think you can give them an answer both satisfying and evasive in such a situation.

DR. YANNET.—I think it is possible to orient the parent to such an extent that he will realize that such a question cannot get too accurate an answer.

DR. STYLIANOU.—Don't you think that with frankness you are going to put your point across much better than if you try to evade the question?

DR. YANNET.—I am sure you get into more trouble if you talk around something instead of saying simply: "This is as much as we can say about the child at the present time."

DR. TARJAN.—The question we now have among ourselves is one of semantics, Dr. Yannet. Dr. Bakwin and I are saying essentially the same thing: we can tell the range of potentialities, but every now and then we have encountered a disturbed parent who was not satisfied with this and tried to ask us more specifically if he will be able to read, write, go to school, do this or that. Answering this kind of meticulous questioning is difficult because the range of potentialities is rather broad, and in this uncomfortable situation we are inclined to speak around the issue a little bit. The plea of each of us is to point out the range of potentialities. What the child will be able to do depends much upon other personality components; and foretelling those personality components in a very young, retarded child is not an easy job. Most parents, I think, will be satisfied with a range answer, such as we can give.

DR. BAKWIN.—Dr. Stylianou, will you go on with your criticisms?

DR. STYLIANOU.—I represent the parents and am giving what the parents have in their hearts. When a doctor diagnoses a case correctly and advises institutionalization in a state hospital because of family or economic situation, it is a severe shock to many parents. Even I sometimes have to tell some parents with retarded children that the best place is the state hospital. I then have to give them a long lecture to try to convince them. They tend to be prejudiced and antagonistic toward the state hospital, because they have a misconception of what it is and believe it is a place where youngsters are placed in padded cells and treated like animals or placed in large groups in dormitories. Parents visualize the worst and naturally would rather slave to keep the child at home, no matter what the sacrifice would be or how disadvantageous this would be to the retarded child. We have two speakers here who are authorities on institutions, and they can give us a picture of what an institution really is today; I know it is not what the parents believe it to be.

DR. BAKWIN.—Dr. Yannet, do you want to tell us what a modern institution looks like?

DR. YANNET.—It would seem unnecessary to tell parents what an institution looks like. You simply invite them to take a look. (Dr. Stylianou: "If you can get them there.") You first should orient the parents as to what to look for in an institution, and once you have given them a few minutes of orientation, you let them visit. It is also advisable to give them an idea of which part of the institution the child will live in. There is nothing more disconcerting than to have a parent examine one of the cottages designed for the high-grade, trainable child and then learn that she has a very seriously retarded child who could not possibly be handled in this type of cottage, thus giving her an erroneous idea of what type of

management her child would be exposed to. Probably the best thing is to invite the parents to look through the cottage and see the type of environment the child will be in.

[There followed a discussion by the panel of ways and means of visiting state hospitals and of the problems involved.]

DR. BAKWIN.—If you had a patient who needed institutional care, why would you send him to an institution if the parents objected?

DR. YANNET.—I really think it is not good medical practice to try to sell a type of service like an institution to a parent. You may feel it is the best place for the child, yet it is almost impossible for a physician to know the details of a home situation, how much it means to the mother to care for the child, and what the relationship is between the father and mother, or to know many of the deep-seated feelings of a parent. One would almost have to psychoanalyze a parent for months before feeling competent to make a decision which is basically one the parents must make. From my own experience I know that the worst mistakes I have seen in the community have been situations where the physicians made the decisions to institutionalize the patients without presenting the facts in a manner allowing the parents to make the decision themselves. You ought simply to present all the facts in the case, the pros and the cons, so that once they have made a decision they know they have evaluated both sides. There we do have a responsibility. My reactions are such that, if I feel a particular child is a terrific problem in the home and should be in an institution, I unconsciously gear my orientation in such a way that it takes a rather dense parent not to get the point. Still it must be presented in such a way that the parents make the decision entirely on their own.

DR. BAKWIN.—Do I infer from anything that you said, Dr. Stylianou, that the parents are coming to feel that the institution is a desirable place for the retarded child?

DR. STYLIANOU.—Some of them are reconciling themselves to the idea except for two points: one is that they expect their children to have a sort of semihome atmosphere in an institution, and, second, they expect an institution to have a training program for the child where possible. Some training should be offered, so that an institution will not be merely a custodial place or a terminal place but a place where the child will be trained and, if possible, eventually sent out into the world. The state of California is providing for foster homes now because of a lack of facilities and, if properly supervised and licensed, I think this can meet the first requisite of a homelike atmosphere.

DR. BAKWIN.—Why are foster homes better than the child's own home?

DR. STYLIANOU.—The child may not be able to live in the home because of economic or environmental conditions, such as other children in the family, or because he has no other children of his own level to play with and is unhappy. In a foster home he will be in a situation where he can play with children of his own level.

DR. BAKWIN.—Would not a more constructive attitude be to try to educate the public to accept the child, and not regard him as a stigma?

DR. STYLIANOU.—That is a very good point. However, there are cases where the child who is retarded cannot really mingle with other children because he cannot compete. But the stigma is one of the cruel things in our society. The public needs to be educated to understand and appreciate these youngsters, and that is one of the main objectives of the National Association for Retarded Children: to educate the public to accept these children as human beings deserving just the same privileges and the same treatment as the so-called normal child.

[There followed a discussion of the aims and activities of the parents' organizations.]

DR. BAKWIN.—It has been very instructive for us to learn of the areas in which parents are critical of us, and three points were made: (1) that we do not give a frank, open statement in regard to the child's condition; (2) that we are not clear about the prognostic possibilities; and (3) that we urge institutional care too strongly.

QUESTIONS FROM THE FLOOR

QUESTION: Can a diagnosis of mongolism be irrevocably made immediately following birth, so that the parents may be informed as soon as possible?

DR. YANNET.—This will depend on the experience of the physician. It can often be made with certainty, but it is never an emergency to make an immediate diagnosis, and if there is the slightest doubt in your mind, you ought to be very careful of how you express the diagnosis to either parent. No great harm is done if you wait until you are a little bit more secure, because if you make the wrong diagnosis it is a terrible mistake.

QUESTION: What do you think of the idea of letting the parents realize there is something wrong with their baby before giving them the diagnosis of mongolism?

DR. KOCH.—Every one of us has to practice the art of medicine, and many times it is as important as the science of medicine. I think each of us has to feel his way with each individual case, and I do not believe you can make any clear-cut rule, but in general if you know the diagnosis is mongolism I do not see what is gained by keeping it from the parents.

QUESTION: Why are physicians reluctant to work with school administrators or special service personnel in the planning for retarded children both educable and trainable?

DR. TARJAN.—Obviously there are some physicians who seem to be reluctant to do this kind of thing. A much closer liaison is needed between physicians and school personnel in general and not only in the field of retardation. One excellent approach to this problem is the kind of institute now being advocated by the American Medical Association concerning physicians and schools. Recently one was held here in Los Angeles. School people and physicians talked together about each other's problems. One of

the reasons doctors are sometimes reluctant to work with school people could be that they do not understand the problems faced by the school people and, vice versa, the latter do not always take into consideration the important role of the physician. I am afraid that we have both school people who do not know how to work with doctors and doctors who do not know how to work with school people.

DR. YANNET.—I was going to reword that question. Why are school people so reluctant to undertake the care of the mentally retarded? There seems to be a tremendous amount of fear of the mentally retarded. They have reached a point where they accept the high-grade type and are willing now to have them in a special class. But when it comes to the middle grade, the mongoloid child, you would think they were going to deal with monsters!

QUESTION: What is being done to educate physicians in understanding the retarded child?

DR. KOCH.—In our Clinic for the Study of Mental Retardation we are including a pediatric resident, if interested. We are not forcing them into it. Next year we are planning to have medical students rotate through our study clinic. Also we are rotating an interested pediatrician through our clinic for a sufficient period to get acquainted with this problem.

DR. YANNET.—At Yale, the students have two seminars devoted to the problems of the mentally retarded. These seminars are prepared by a group of students under the supervision of a senior member. All of the medical students have a visit to Southbury, where they get some degree of orientation and see the functioning of an institution. We have an elective course for senior medical students in our clinic and the outpatient department, which sees a large number of mentally retarded children. Every pediatric intern at Yale rotates through Southbury for two months. That is a regular part of the pediatric training program and there is a resident who spend six months at Southbury.

DR. TARJAN.—The faculty at the University of California at Los Angeles Medical School is giving more and more emphasis to the understanding and the education of the medical students in the field of mental retardation. During the family medicine course and during the pediatric clerkship they have a chance to work in the field of mental deficiency. I want to emphasize something much more important and that is the role of an institution for the mentally retarded in the education of medical students and postgraduate students. There are three medical schools in this area; two of them send their students to our place at the present time, and also their residents, on a rotation basis.

DR. STYLIANOU.—The National Association for Retarded Children is planning to provide scholarships to interns or medical students so that they may specialize in some phase of mental retardation.

QUESTION.—If the parent shows an obvious need for continued help with his own emotional reactions and conflicts about bearing a mentally retarded child, how do you handle the

interpretation of the degree of retardation, and what use do you make of your own community family counseling service, etc.?

DR. TARJAN.—I would like to place the parents into two therapeutic groups: first, those in whom the problem does not seem to be a deep-rooted one. For them the problem can be approached by focusing essentially on the child's problems. Second, the parents with emotional problems much more deep seated. For them the conflict involved in the retarded child is purely a symptom of the deep-seated emotional problems they had to begin with. This group obviously needs to be referred to psychiatric help. In the first group we have found that our own clinic caseworkers and caseworkers in family service agencies do a top-notch job in focusing the parents' attention on the problem that produced most of the conflict in them, and the solution to the problems of the child usually lessens the emotional turmoil in the parent.

QUESTION FOR DR. KOCH.—Do you specifically recommend your parents of newly studied patients to join a parents' group?

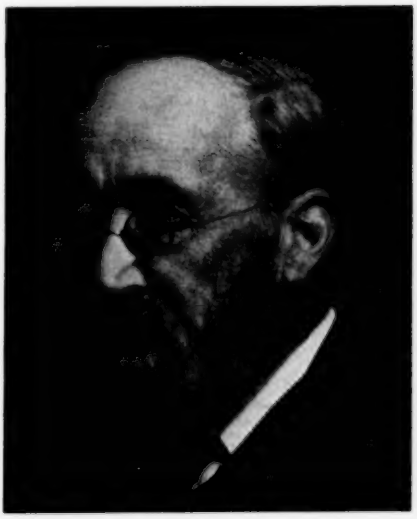
DR. KOCH.—The answer is "yes." It is a good psychological experience for parents with similar problems to get together.

DR. BAKWIN.—Do you want to amplify this, Dr. Tarjan?

DR. TARJAN.—One of the first issues arising in a family after diagnosis is made is that they have been singled out as the only ones to have this tragedy. Their first comforting experience is to meet other people with similar problems and, more important, to find out that the problem can be handled. This I think is a crucial benefit they derive from a parents' organization.

Pediatric Profiles

John Thomson
(1856-1926)



JOHN THOMSON as a pediatrician may come to be forgotten. Yet in his generation he was eminent among British pediatricians, and his name was also often on the lips of medical men throughout Europe and America. His fading memory may be the result of several causes. His textbook on *Diseases of Children,* famous in its day, was up to date in 1926 (fourth edition), but is out of date today. His shyness precluded his success as a teacher. In his writings his modesty made him play down his own part in the subject under discussion. Interested as he was in medical politics and medical affairs, he took a very small part in either. Yet in his day, that is, in the years from his graduation in Edinburgh in 1881 to his death in 1926, John Thomson along with Thomas Barlow and George Frederic Still were the three outstanding leaders of British pediatrics.

BRITISH PEDIATRICS, 1881 TO 1926. THE TRIUMVIRATE

The dates 1881 to 1926 are perhaps an artificial division of time in medical history. But they mark off a period of pediatric history in Britain which can be truly called great. Back two hundred years, Dr. Thomas Browne of Norwich, writing of the medicine and natural philosophy of his own day, described them in his rich style as "verities yet in their chaos." Well, if you think of the following subjects in the pediatric corner of the medical field in 1880—viz., rickets, scurvy, infant nutrition and digestion, pyloric stenosis, juvenile rheumatism, the different forms of meningitis, the heap of congenital structural defects, and the great host of others—you will agree that at the beginning of our chosen period these pediatric verities were either in their original chaos or taking only an indistinct shape in the void. There were also big changes in the conditions of study of pediatrics;

in the fifties, separate hospitals for the study of disease in children had been set up in Britain; and for thirty years general physicians had served in these new hospitals and had laid down some kind of foundation of theory and practice before passing on to become physicians and consultants in general hospitals. For medicine and surgery, 1880 began a new age. But in pediatrics it was more than that. It was a new creation in the medical world and represented the neonatal period of a new medical creature, the pediatrician.

In 1881 Thomas Barlow was in his prime, at 36, at Great Ormond Street Children's Hospital, having written valuable papers on diseases of children; and now putting the final touches to his article on infantile scurvy which was to see the light of print in 1883 and to take its place among the medical classics of the world. In the same years John Thomson graduated in Edinburgh and came to Great Ormond Street in 1884 as resident physician, remaining there for two years, while in 1881 George F. Still was a boy at school in London, a clever studious boy specially fond of the Greek lessons. These three persons were to become close and lifelong friends. Barlow and Still each had long service in Great Ormond Street. Thomson's service there was short but significant. These three men were to become the triumvirate of British pediatries in the succeeding generation. I am careful to use the word British, for if you used English or Scottish, you would run into trouble. The word British applied to these three men as a common geographical label, for the oldest was a genial, rugged, Lancashire man, the youngest a shy and rather touchy Cornishman, and Thomson a shy and gentle Lowland Scot. All three were born and nursed in British medical schools.

With this skeleton of general and pediatric medical history, I now turn to John Thomson. I shall present his profile (not a fully drawn portrait), and try to justify his inclusion in the British triumvirate of pediatricians, whose work and influence during their lives gave them a lead among many fine workers in Great Britain and Ireland at this time.

John Thomson was a clinician of rare qualities; he was a poor teacher in the ordinary sense of *talking;* the fruit of his work was to be found in his articles in medical journals and especially in his book ***The Clinical Study and Treatment of Sick Children.*** His outpatient clinic at the hospital became known as "The Mental Clinic" because of the large number of mentally defective children it contained. When retired from hospital practice, he continued this Clinic until his death. Later I shall try to give a picture of Thomson at work in it.

The man himself, in his outward appearance and manners, was morbidly shy and often silent. He was shortsighted, and his thick lenses together with his silences hid his merits from his teachers in the early days at Great Ormond Street and throughout his life from his colleagues in Edinburgh. Some mothers (not many) may have taken his silence for ignorance. But he was indifferent to this lack of appreciation or approval. Indeed in the midst of these silences

his powerful mind was in full operation, grinding away, or (with a change of metaphor) chewing the cud of fancy.

JOHN THOMSON: "THIS DREAMER"

The brothers of Joseph, with his dreams of domination, said one day: "Behold this dreamer cometh." Now John Thomson was a different kind of dreamer; he was of the order of contemplatives, and when he was silent his mind was usually in intense action. But he was often misunderstood and undervalued. This was seen in his two years of internship at Great Ormond Street and testified to in 1929 by Sir Thomas Barlow forty years later in a memorial address in Edinburgh. It was a public recantation of his first unfavorable impression of John Thomson, then resident physician under Barlow. I quote Barlow's words: "I confess that at the outset of our acquaintance I was not impressed by his personality; and some of the juniors on the staff, and of his contemporary residents esteemed him but lightly. We little knew what a reserve of quiet power, sound method and good judgment lay beneath that modest half-deprecating manner." Three years after this early contact, Thomson published his translation of Henoch's *Diseases of Children* and followed this by a series of masterly articles on various subjects; and Barlow became and remained a close and admiring friend of his shy young intern. Although Thomson grew in confidence from the wide recognition of his published work (articles and books), his shy, silent behavior remained throughout his life. An example of this inveterate habit of his mind was given to me in 1908 when I was his resident physician at the Sick Children's Hospital in Edinburgh. During a ward round I asked him to auscultate a child's heart which puzzled me. At once he bent down, applied his short wooden stethoscope, and listened long and earnestly. When it was over, he said nothing, and the ward round proceeded. After three or four beds had been passed, I had to ask him his opinion of that heart. He looked at me, that well-known look of innocence and candor, and said: "Oh! I wasn't listening!" He then went back to the bed, and applied his stethoscope again, this time with a *hearing* ear.

This incurable habit of dreaming does not explain his shyness with ordinary people and with ordinary audiences. Dreamers can be very good talkers, as Joseph probably was. The shyness may have begun with some unhappiness in childhood; he confessed this to his family but never disclosed the cause. But it was no hindrance to his making many personal friendships in Britain and America.

"THE GENIUS OF FRIENDSHIP"

These were the words used by Barlow in the memorial address. Thomson seems to have been the magnet which ensured the success of the London C.C.C. (the letters stood for Children's Clinical Club), which flourished in the last decade of the old century and the first decade of the new. Dr. H. C. Cameron, one of the early, though not original, members, had said that the London members would turn out in strength if they heard that John Thomson was to be there, so that they might hear him talk. Many of his later and close friends first met him at the C.C.C., held in the dining

rooms of the London members. In the last edition of his book Thomson gives a list of his "inspiring teachers": "Henry Ashby [Manchester], Thomas Barlow [London], Byrom Bramwell [Edinburgh], D. B. Lees [London], James Mackenzie [Burnley], William Osler [Baltimore and Oxford], Eustace Smith [London], L. Emmett Holt [New York], and Professor Henoch [Berlin]." That is a distinguished international list; and is given, with characteristic care, in alphabetical order. In fact he came to have many friends among seniors, contemporaries, and younger pediatricians. In his profile of Leonard Findlay in THE JOURNAL OF PEDIATRICS, Stanley Graham tells how he and Findlay used to motor on Sunday afternoons over the long Scots miles that lie between Glasgow and Edinburgh, and sit down with John Thomson at his fireside for talks that ranged beyond pediatrics.

The recognition of his work abroad gave Thomson deep satisfaction, and the early conferment upon him in 1903 of honorary membership of the American Pediatric Society brought him personal friendships in the United States which he valued greatly. I remember his unstinted admiration for Emmett Holt's second edition of his textbook, and years later I had the pleasure of greeting Holt (senior) on the doorstep of John Thomson's house in Edinburgh. His friendship with Holt was based on something more than admiration for his book; there was much affinity of character between the two men. On Thomson's mantelpiece in Coates Crescent, Holt's photograph was placed in the central position of honor above other objects—a symbol of Anglo-American friendship.

I have emphasized the friendship side of Thomson's character to make it plain that he was no self-centered recluse; on the contrary, his life was rich in friends. Three years after his death, Sir Arthur Keith, Hunterian Professor, Royal College of Surgeons, England, wrote these words about John Thomson: "He was the most lovable, kind, and wise of all the physicians I have known. He enriched medicine by example as well as by precept."

CLINICIAN AND BOTANIST

John Thomson was off-center (eccentric) in his shyness and absentmindedness. He was also not entirely on-center in the outward activities of his medical mind. To be fair, he might be called a poor teacher of students at the bedside and in the lecture room. This defect was very noticeable in a medical school in which there were excellent and even outstanding teachers. But once he had proved his worth by his writings, his colleagues agreed that his learning was there but could not be imparted by word of mouth.

He was a consummate clinician: in the great store of his clinical material, in his accurate observation, recording, and filing; in the long follow-up of special cases; in the free use of photographs; and in his zeal for postmortem examinations. In the last matter, so great was his zeal that often in his early years he carried out his own autopsies on the kitchen tables of the Cowgate and Canongate (the poor districts of Edinburgh). All these records, with their registers, were done by his own pen, without secretary or typewriter.

He was mainly a clinician of outpatients. This great store of records was begun in 1886 at the New Town Dispensary, Edinburgh, and it continued without a break, either there or at the Children's Hospital, until a week or two before his death in 1926. It was therefore an unbroken stretch of forty-one years' work, first at the Dispensary, and then at the Children's Hospital; and it was a Children's Clinic, mainly so at the Dispensary and entirely so at the Children's Hospital. Of course he threw away the dross, but he kept every kind of precious metal. The character of the material was influenced by his close association with Byrom Bramwell from 1886 onward. It was rich in dwarfs of many kinds, and in rare congenital and hereditary conditions. His clinical predilections were fairly wide, and in his Clinic he would often snap up a pylorie stenosis as well as a cretin. Byrom Bramwell produced his *Atlas of Diseases*. For Thomson, his Clinic represented the loose pages of an album of flowers and specimens of children's disease.

It is significant that at college Thomson was a keen botanist. A college friend said that Thomson was much alone in his spare time, going about by himself on lonely walks, looking for flowers and plants, with his eyes bent on the ground. He carried this habit of mind into his lifework as a clinician, both in his hospital ward and in his Children's Clinic. While quickly recognizing the usual, he was swift to see when anything unusual or rare was before him in the procession of child *plants* that came under his eyes. Just as an expert gardener can tell in the dark by the feel of a single feature that that apple is a Newton Wonder and that a Keswick Codlin, so Thomson botanized among his d i s e a s e d child-plants, searching over every part of the body for some telltale abnormality in head, face, eyes, ears, hands, etc., and quickly deciding that this was an achondroplasia, that a mild cretin, and the other a mongolian defective.

At the sessions of the Clinic, nearly all the talk was between Thomson and the mother, and very little between the physician and his audience of one or two. We came to accept the position that he was not going to talk to us, but that he was glad that we should watch him practice the art of the clinician. Since 1904, that is, twenty-three years before his death, the Clinic came to be known as the Mental Clinic, and to have a preponderance of three groups of cases: (1) the nervous child, (2) the dull or retarded child, and (3) the mentally defective child.

THE MENTAL CLINIC. A ROUTINE SESSION

In his Morison Lectures (1924) Thomson summarized his own case notes of 1,200 children, all under 5 years when first seen and including private and hospital cases. Of these, 952 were mentally defective. I mention the figures simply to show the magnitude of the new medical task he had set before him and the greatness of his own contribution to it. This colossal study of the mentally defective baby and young child was the last of his medical enterprises; and it was the greatest, and most difficult. If he left it unfinished or only begun (as he said), he showed a good way of continuing it.

I attended many sessions of the Clinic, and shall finish this brief profile of John Thomson by describing him at work in it, face to face with the mentally defective baby and the distressed and anxious mother. The clinician sits in his chair at the side of a table, with that air of benignity and calm that is always about him in a clinical operation. Opposite is the mother, with her baby restless and crying on her lap. Sitting beside them are the teacher of a nursery school and myself; silent watchers of the scene. A nurse stands at the table, a silent and active assistant. There are two other pieces of "furniture." On the table is a small German musical box; and behind his master's chair lies a small dog with sharp eyes and ears cocked (name, Skippy). The session begins with a history of the family, the child, and the illness, and many et ceteras, given by the mother and written down by Thomson on his case paper in a legible longhand. A searching but rapid examination follows. Then the diagnosis is written in, is translated to the mother, and instructions for treatment given to her in the simplest terms. Three or four cases, new or old, follow and are dealt with in the same routine. The clinical instruments of the musical box and the hidden dog are only used in exceptional cases. When the child was noisy and refractory, Thomson would lean forward and release the catch on the musical box and at once the sweet strains of a German song would steal upon the clamor.

"In sweet music is such art,
Killing care and brief of heart."

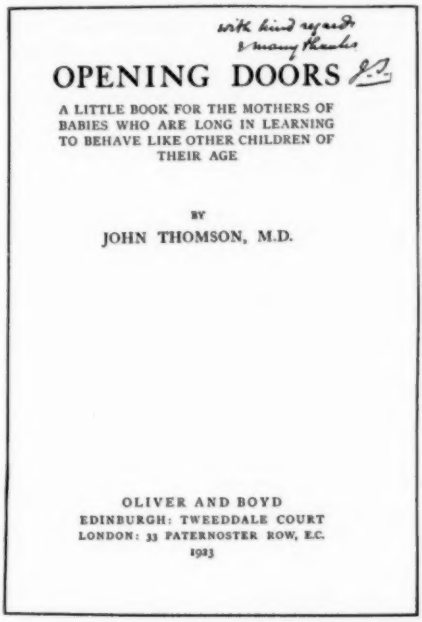
This would often charm the child into silence, but sometimes would fail. If the child were very vacant and dull, Thomson would use the dog. Placing a chair beside him he would give Skippy a signal. At once the mongrel terrier (of Schuperke breed) would spring lightly on the chair and look earnestly at the child, showing his hairy muzzle and his bright friendly eyes. Skippy never barked, but stared at the child with curiosity and doggy goodwill. It was an eloquent look. Sometimes it brought a sparkle of interest and animation to the vacant eyes of the baby, even a smile, and sometimes there was no response; but I never saw a dull baby frightened by Skippy. These two unusual clinical tests usually aided prognosis.

The 952 cases of mental defectives, all first examined when under 5 years of age, and presented in the Morison Lectures of 1924, came mainly from the Mental Clinic at the Children's Hospital. The Morison Lectures were published in the *Edinburgh Medical Journal*, May, 1924. For this profile, I thought it would be of interest to give, as I have done, a picture of the Mental Clinic at work.

"OPENING DOORS"

We all know the difficulty the physician has in speaking to the mother of a mentally defective baby or young child; not only in explaining the diagnosis but in advising about education and management. In 1923 John Thomson wrote a little brochure on the subject. This was addressed to mothers, written in the simplest words and giving instruction in the management of the many different kinds of mental and physical debility. This brochure, called *Opening Doors*, had a subtitle, *A Little Book for the Mothers of*

Babies Who Are Long in Learning to Behave Like Other Children of Their Age. The title page is followed by nineteen pages of text with index. Published in 1923, it is still in circulation among mothers in Great Britain and Ireland. It is written in words that can be understood by all who have learned to read. It tells the mother


with kind regards
& many thanks
J.T.

OPENING DOORS

A LITTLE BOOK FOR THE MOTHERS OF BABIES WHO ARE LONG IN LEARNING TO BEHAVE LIKE OTHER CHILDREN OF THEIR AGE

BY

JOHN THOMSON, M.D.

OLIVER AND BOYD
EDINBURGH: TWEEDDALE COURT
LONDON: 33 PATERNOSTER ROW, E.C.
1923

all she needs to know, and all *she* can do for the mentally defective child (whatever the type of defect). Its author is a physician who has given a lifetime to study of the subject. It must have given comfort, encouragement, and practical guidance to thousands of such mothers.

The Mental Clinic showed John Thomson in the fullness of his powers, as a scholar, physician, and humanist. He was engaged in one of the major problems of pediatrics, that of mental defect in infancy and early childhood. His contribution to it was immense in the time and labor given to it and in the motives of understanding and compassion that inspired all his efforts. His span of life of seventy years was too short; had it been seven times seventy, it still would not have been enough. He knew that well, and said it was only a beginning. But it was so beautiful in its craftsmanship and so noble in its ethical motives that it might be called John Thomson's Unfinished Symphony.

Charles McNeil

Comments on Current Literature

VARICELLA PNEUMONIA

UP TO 1955 only about fifteen well-documented cases of varicella pneumonia had been recorded in the literature. Within the past few months, however, several reports have appeared in current journals, indicating that varicella pneumonitis may be more common than was supposed previously, and that mortality from this complication of chicken pox is significant. In a series of patients reported in 1935 which numbered 2,534, there were twenty-one instances of complicating pneumonitis.[1] Apparently only one case of varicella pneumonitis has been described in a child, a 5-year-old girl.[5] All of the other cases reported in the medical literature occurred in adults, as did the currently recorded cases: predominantly in young adults, with a few exceptions in which the condition occurred in older individuals, 42, 46, and 71 years of age.

Signs of pneumonic involvement develop typically on the second to the sixth day after the appearance of the rash, which in the instances recorded has been invariably extensive, and in some patients was described as "almost confluent." Temperature is usually high, and the patients show varying degrees of cyanosis, dyspnea, with cough producing bloody sputum. Chest pain may be a prominent symptom. Marked improvement in the pneumonic involvement is usually apparent within from two to seven days; however, involvement may be widespread and manifestations severe, progressing rapidly to fatal outcome. In general, diminution of pulmonary signs and symptoms coincides with subsidence of the cutaneous eruption and the disappearance of lesions from the membranes of the mouth and throat. Generalized lymphadenopathy, which may be quite apparent, subsides slowly.

The pathologic findings include swelling, proliferation and desquamation of the alveolar septal cells, accompanied by mononuclear cell infiltration. In typical cases areas of necrosis and hemorrhage are observed in the lungs with little or no evidence of bacterial infection. Type A intranuclear inclusion bodies characteristic of varicella and herpes zoster have been seen in macrophages, in septal cells, and in the cells of the bronchiolar epithelium. The roentgen findings are those associated with a diffuse, finely nodular pulmonary infiltration. These nodular infiltrates vary in size but appear larger than those which characterize miliary tuberculosis. While complete clearing of the pulmonary lesions usually takes place within three to four weeks following onset of illness, persistence of roentgenographic findings has been reported in some instances for as long as three months. The varicella is often that occurring in young adults, usually parents who have been exposed to children with chicken pox. In most cases the adult became ill within about fifteen days following exposure to children with clinical disease, their own children, or those closely associated.

In the November, 1956, issue of the *American Journal of Medical Science,*

Fitz and Meiklejohn[2] report an unusual experience with eleven cases of varicella complicated by pneumonitis. Three of these eleven patients, seen during the past five years, had a fulminating clinical course with fatal outcome. One of these, a father 35 years of age, had been exposed to his children with varicella two weeks prior to the onset of his illness. He became rapidly and acutely ill, and died within four days following the appearance of the exanthem. The course in this patient was so fulminant that he died en route to the hospital. The pathologic findings included a widespread hemorrhagic pneumonitis, interstitial myocarditis, and an acute lymphadenitis. Type A inclusion bodies were observed in desquamated alveolar septal cells. In another instance a 29-year-old father, whose child had varicella at the time, developed a productive cough and dyspnea on the third day of his exanthem. During the night following, the dyspnea increased progressively; he sat up in a chair in the living room where he was found dead at an early hour the following morning. Post-mortem examination revealed a hemorrhagic pneumonitis, pleural lesions of the type seen in visceral chicken pox, and varicelliform lesions in the pharynx and esophagus. Type A intranuclear inclusion bodies were observed in the cells of the esophagus. In the third fatal case reported by these authors, the history, clinical course, and pathologic findings were similar except that there was even more evidence of visceral invasion, necrotizing lesions being observed in the liver, kidney, and spleen. Type A intranuclear inclusions were identified readily in microscopic sections of skin and liver, as well as in the alveolar septal cells.

Another group of patients with varicella reported by Fitz and Meiklejohn[2] experienced severe clinical manifestations but survived; these patients had signs and symptoms of pneumonitis, and x-ray examination of the chest revealed diffuse nodular infiltration throughout both lung fields. All the patients in this group were gravely ill for about four or five days, but eventually recovered under symptomatic therapy, which included oxygen, antibiotics, and, in one instance, hydrocortisone. One of the patients in this group was a mother, 25 years of age, who was three months pregnant at the time of onset. She developed severe pneumonitis and was in acute respiratory distress, using accessory muscles in order to breathe, and deeply cyanotic when not receiving oxygen. In addition to oxygen, antibiotics, intravenous hydrocortisone and oral cortisone were administered, and the patient eventually recovered. On the seventh day of her illness vaginal bleeding occurred with threatened abortion, which was averted; subsequent convalescence was slow, but uneventful, until the sixth week following the onset of the varicella, when abortion of a four-month macerated fetus occurred.

In these eleven cases, constituting the experience of the authors, roentgenographic findings are emphasized. Although the clinical manifestations of pneumonitis might appear minimal, especially early in the illness, x-ray examination of the chest revealed a diffuse nodular infiltration which was striking, and which seemed to be out of proportion to the manifestations demonstrable by physical examination. These pneumonic findings tended to persist for weeks, or in some instances for months. While no virus was isolated in any of these studies, the presence of type A intranuclear inclusion bodies in the tissues of the three patients who came to necropsy seems to support the clinical impression of varicella complicated by pneumonitis. In one case, a patient who recovered, the severe manifestations and the widespread,

almost confluent eruption suggested the diagnosis of variola. However, vesicular fluid from the lesions inoculated into the embryonated hen's egg gave no evidence of growth on the chorioallantoic membrane, which is highly susceptible to invasion by the virus of smallpox in contrast to that of chicken pox. Subsequently two nurses who were exposed to this patient developed typical varicella, thirteen days and sixteen days following the exposure.

In the *Annals of Internal Medicine*[3] (September, 1956) a case report appears in which "primary varicella pneumonia" is described in a young adult male who was admitted to a United States Army Hospital. He had been exposed to his own three children, all of whom had had chicken pox over the six-week period just prior to the father's illness. The clinical course in this patient was very similar to that described by Fitz and Meiklejohn, with extensive rash and high fever, and, beginning on the sixth day, chest pain with severe productive cough and roentgenographic evidence of diffuse pulmonary involvement. Other single case reports have appeared in recent months, two in *Radiology*[4] for May, 1956.

The *American Journal of Roentgenology* for September, 1956, carries two articles dealing with "primary chicken pox pneumonia." Sixteen cases are reviewed by Tan, Kaufman, and Levene,[5] with excellent reproductions demonstrating the characteristic roentgenographic pattern. The lesions are described as ". . . widespread nodular densities superimposed on markedly increased bronchovascular markings. These infiltrates varied in size and though some were sharply defined from the surrounding lung, others seemed to merge with the adjacent tissue."[5] This miliary distribution was considered characteristic by the authors, readily differentiating varicella pneumonitis from the secondary bacterial pneumonias in which the distribution tends to be patchy.

In the same issue of the *American Journal of Roentgenology*, x-ray findings in chicken pox pneumonia are reported by Southard,[6] based on experience with five cases. Differential diagnosis on roentgenographic grounds between varicella pneumonia and other types of pneumonitis is emphasized likewise by this author, who states that the "diagnosis can be made by the roentgen demonstration of an acute diffuse miliary pneumonia in association with the skin lesions of varicella."[6]

While, as a rule, varicella does not seem to be a severe disease of childhood, these reports indicate that it may be a very serious, and, in some cases, a fatal disease, if contracted by adults, often parents of children who are experiencing the usual mild to moderately severe infection commonly seen during childhood. Adults who contract varicella should regard the disease in themselves as a serious medical condition, and medical attention should be sought promptly in order to avoid possible serious complications. With prompt recognition of complications in the adult, immediate use of symptomatic treatment, such as oxygen, good antibiotic coverage to avoid secondary bacterial invasion, and supportive measures, such as the administration of fluids, cortisone, where advisable, etc., might go a long way toward the prevention of fatal outcome. With improved laboratory techniques, notably tissue culture, the presence of varicella virus can be detected more readily. It is now possible to establish a definite etiological basis for this disease, and it is hoped that, as more is known about the nature of the infectious agent, an effective vaccine may be possible for the protection of adults. Such protection might be particularly helpful in the case of the pregnant woman, since in at least one recorded instance[2] termination of the

pregnancy apparently resulted from severe varicella infection occurring toward the end of the first trimester of pregnancy.

RUSSELL J. BLATTNER

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Correspondence

To the Editor:

I too have been asking myself whether medical meetings are worth while. I am referring not only to International Congresses, but to the national and even local meetings. With the tremendous increase in the number of publications both of a general and specific nature, it hardly seems worth while to devote an entire evening traveling to and from a medical meeting in order to hear something new, when in the comfort of one's home and with a minimum expenditure of time and effort, one can read this same material and skim over the nonessential or irrelevant material. Moreover, staff conferences at most hospitals have so increased in the excellence of their preparation and the thoroughness of presentation that they can well take care of the purely clinical postgraduate education every physician requires.

One of my "gripes" about the large national meetings is the manner in which the same names from the same institutions appear repeatedly on the program. Surely there are other men in pediatrics doing a good job in pediatric surgery, or pediatric allergy, or pediatric rehabilitation, or pediatric neurology, or any other of the pediatric specialties who also should be heard from. The journals are full of papers from good people in good institutions, but the speakers at our national meetings seem to come from a pretty selective small group.

On the positive side I agree with you on all the benefits to be derived from attendance at these meetings, although I too must confess that I rarely meet a familiar face in the large morass of unfamiliar ones. An additional factor which you did not mention is the psychologic one which the physician experiences from being part of the main stream of medicine when he attends the large meetings. The prosaic problems of day-to-day practice seem a little less prosaic, and the nagging questions seem a little less nagging, when one has had three or four days in the current of advancing medical science. One returns refreshed, as undoubtedly does a pious layman after a three- or four-day period at a religious retreat.

ABRAM KANOF, M.D.
Brooklyn, N. Y.

News and Notes

Dr. Joseph B. Pincus has been appointed full-time professor of pediatrics at the State University of New York College of Medicine in Brooklyn, N. Y., and director of pediatrics at the Jewish Hospital of Brooklyn.

The 52nd annual meeting of the **American Trudeau Society** medical section of the National Tuberculosis Association will be held in Kansas City, Mo., May 6 to 9, 1957, in conjunction with the annual meeting of the National Tuberculosis Association.

The **Merrill-Palmer School** in Detroit announces a new graduate and postgraduate program of research training in human development and family. One-year programs designed to supplement graduate training in psychology, sociology, education, and home economics will offer students supervised research experience in an ongoing project or in one initiated by the student. The direct research activity, comprising over one-half of the student's time, will be combined with course work including an advanced seminar on the role of theory and method in research in human development and family life and elective courses. Fellowships are available with stipends from $1,000 to $2,500. Applications will be acted on beginning March 1. For further details write to: Dr. Irving Sigel, Merrill-Palmer School, 71 E. Ferry Ave., Detroit 2, Mich. For information on fellowships write to the Registrar at the same address.

Residency positions are available in *Pediatric Pathology* at **The Children's Hospital of Philadelphia** for the year 1957-1958. The Department of Pathology is closely affiliated with the School of Medicine and Graduate School of Medicine, University of Pennslyvania. The residency program provides for experience in anatomical pathology and research. Residents are also encouraged to participate in clinical conferences, ward rounds and clinics. A limited number of fellowships are available for research in pediatric pathology. Candidates should have completed at least one year of residency training in pediatrics or one year in research. Address inquiries to: Bernard M. Wagner, M.D., Department of Pathology, The Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46, Pa.

A refresher course in *Pediatrics* will be conducted at **St. Christopher's Hospital for Children**, Philadelphia, by the Pediatric Department of Temple University School of Medicine on May 22 to 25, 1957. Each half-day session will be devoted to a single phase of pediatric medicine. For information regarding enrollment, registration fee, etc., write to Dr. John B. Bartram, St. Christopher's Hospital for Children, 2600 N. Lawrence St., Philadelphia 33, Pa.

The **Academy of Medicine of Cincinnati** will hold its 100th Birthday Party, Feb. 27 through March 5, 1957. In order to officially observe the occasion, a Health Museum and Exposition will be established in Cincinnati's spacious and historic Music Hall. One hundred seventy-five health and scientific exhibits, representing medicine, hospitals, research centers, public health, nursing, pharmacy, and industry will be displayed in the north and south halls. Notable among these exhibits and occupying some 4,000 square feet of space will be

an atomic energy exhibit from the American Museum of Atomic Energy entitled "Atoms for Peace." Dr. Paul D. White and Dr. Walter Alvarez, noted medical scientists and authors, have accepted invitations to be among the distinguished guest speakers. The Centennial Convocation will be held on the last night of the Exposition, March 5. The Convocation address will be given by Sir Edward Appleton, Nobel Laureate, Edinburgh, Scotland. Civic leaders, officials of both the American and state medical associations, and Government dignitaries will take part in the elaborate ceremonies.

The twenty-fifth annual series of the **Benjamin Knox Rachford Lectureships** will take place in Cincinnati, Ohio, on Wednesday and Thursday evenings, Feb. 13 and 14, 1957, at 8:30 P.M. Dr. Alfred H. Washburn, Director of the Child Research Council in Denver, Colorado, will deliver these lectures in the auditorium of the Children's Hospital Clinic and Research Building. The general title is "The Child as a Person Developing." On February 13 Dr. Washburn will lecture on the "Philosophy and Development of a Research Program," and on February 14 the subject will be "More Questions Raised Than Answered."

Harvard University School of Public Health *Public Health Scholarships* for the academic year 1957-1958 will be granted to persons of high professional promise in awards, ranging from part tuition to tuition plus a stipend, according to the qualifications and financial needs of the applicants. The scholarship funds are limited and are primarily intended for citizens of the United States. In general, preference will be given to applicants under 35 years of age.

Scholarships are available to those in the following categories who wish to obtain postgraduate education in the field of public health or in one of the basic sciences related to public health: physicians, dentists and veterinarians; industrial physicians; public health nurses with a college degree and satisfactory field experience; social workers with a master's degree from an approved school of social work and acceptable experience in the field of medical or psychiatric social work; health educators with a college degree, training either in health education or in the natural and social sciences and experience in general education or community health work; dietitians with a college degree and satisfactory field experience; college graduates who have concentrated in one of the natural sciences or in engineering (environmental aspects), for example, biologists, biochemists, nutritionists, microbiologists, parasitologists, or biostatisticians.

Scholarship applicants must be eligible for admission to the school as a candidate for one of the following degrees: Master of Public Health, Doctor of Public Health, Master of Science in Hygiene, Doctor of Science in Hygiene, Master of Industrial Health.

A catalog of the school, admission, and scholarship applications, and further information may be obtained by writing to the Secretary of Admissions and Scholarships, Harvard School of Public Health, 55 Shattuck St., Boston 15, Mass. Scholarship applicants must return completed admission and scholarship applications to the Harvard School of Public Health by March 1, 1957. Scholarship awards will be announced May 1, 1957. Under exceptional circumstances awards will be made at other times.

Books

Practical Pediatric Dermatology. Morris Leider, M.D., St. Louis, 1956, The C. V. Mosby Co., 433 pages. Price $10.50.

A text by the associate professor of dermatology at the New York University Post-Graduate Medical School in New York. Dr. Leider has produced an excellent, practical text and has not "written down" to the pediatricians. After a discussion of the basic scientific aspects of dermatology and the principles of dermatologic diagnosis, a section is introduced on different colored paper containing a formulary of 101 dermatologic preparations for topical application. These are numbered and annotated, and in the remainder of the book (about three-quarters), containing specific discussions of the dermatoses found in children by cause, such as fungous infection, viral infections, pyogenic bacteria, allergic mechanisms, etc., these prescriptions are referred to by the number in discussing treatment. The discussions in this part of the text are excellent and clear. There are 280 unusually good photographs of skin lesions in the text and thirteen drawings. The author has an unusually good style in his writing and has a way of driving home important points in pithy sentences. If there is any criticism from a pediatric standpoint it lies in the fact that the author has omitted from his index colloquial pediatric terms such as "diaper rash," which is probably the most frequent dermatologic condition the pediatrician encounters today. He will find the discussion under the dermatologic term "intertrigo." The volume can be highly recommended to the practitioner as a most useful and practical text for reading and for reference.

Pre and Postoperative Care in the Pediatric Surgical Patient. Edited by W. B. Kiesewetter, M.D., Chicago, 1956, The Year Book Publishers, Inc., 347 pages. Price $7.00.

Sixteen members of the faculty of the University of Pittsburgh School of Medicine have contributed to the text. The first section contains chapters on preoperative conditions, including the child's reactions to surgery, electrolyte balance, and anesthesia. A second section discusses general postoperative considerations, including complications, care of the wound, and oxygen therapy. These constitute about a third of the volume. The third section takes up specific pre- and postoperative details in the various subfields of surgery: abdominal, thoracic, orthopedic, neurosurgical, plastic, urologic, otorhinolaryngologic, and ophthalmic. Each is presented by a specialist in the particular field. The Editor has been most successful in bringing about a uniformity in the various presentations. Each discusses the specific surgical condition in his particular field under the following headings: required studies (diagnostic); elective studies, differential considerations; preoperative management, operative objectives and methods; postoperative management; complications. The discussion in this way is distinctly didactic and cursory. The book will be of interest and service to the surgeon and surgeon-in-training, particularly as a text for rapid reference. It is well illustrated.

Handbook of Pediatric Medical Emergencies, ed. 2. Adolph G. DeSanctis, M.D., and Charles Varga, M.D., St. Louis, 1956, The C. V. Mosby Co., 389 pages. Price $6.25.

The first edition of the text on pediatric emergencies published in 1951 was unusually well received. Not only was it reprinted four times, but was translated into Turkish and Spanish. The new edition has given the authors the opportunity to make numerous revisions. New chapters have been written on Metabolic Emergencies, Accident and Poison Prevention, Genitourinary Emergencies, and Respiratory Paralysis in Poliomyelitis. Much of the remaining text has been rewritten, and additions made to the list of household poisons. New references to discussions appearing since 1951 have been added. The subject is a most

important one, as what to do in an emergency cannot be put off by the practitioner until a thorough study of the literature has been made. While undoubtedly different methods are used in other clinics for certain emergencies, the authors have wisely stuck to the methods they have tried and found successful in the University Hospital, New York University-Bellevue Medical Center.

Pediatrics. Donald Patterson, M.D., and John F. McCreary, M.D., Philadelphia, 1956, J. B. Lippincott Co., 654 pages. Price $14.00.

The appearance of a new textbook of pediatrics is always of interest. This new text, edited by Drs. Patterson and McCreary of the University of British Columbia, has thirty-six contributing authors, chiefly from the medical schools in Western Canada and a few from medical schools in the Eastern part of the country. In size, the volume is about one-half that of such standard texts as Nelson, and Holt and McIntosh. Its stated purpose is "to fit between the excellent volumes which serve as consultant texts for pediatricians and the well-prepared small books of a more tabular style which have become available in recent years. . . . It is designed primarily for the physician in the general practice of medicine. . . ."

We feel the Editors have carried out this rather difficult task in a very satisfactory way. It is not a reference book, but rather a well-written, straightforward presentation of pediatric conditions and diseases in the light of present knowledge. We note no important differences between pediatrics as it is taught and practiced in Canada and in the United States. We feel there is need for texts of this type and that there is a definite place for the text. The book is excellently printed and the nearly two hundred illustrations are good and to the point. Many of the charts and tables are quite original and quite instructive. Other pediatricians who have gone over the volume agree with the reviewer that it is an excellent text.

Common Contagious Diseases, ed. 5. Philip M. Stimson, M.D., and Horace Louis Hodes, M.D., Philadelphia, 1956, Lea & Febiger, 624 pages. Price $8.50.

The fifth edition of Stimson's standard manual of common contagious diseases, first published twenty-five years ago, marks the association of Dr. Horace L. Hodes, in charge of pediatrics at the Mt. Sinai Hospital in New York, as joint author. The picture of the common contagious diseases has undergone marked changes since the text first appeared. This is particularly true of the period since the fourth edition in 1947. The authors have brought out an extensively revised text to keep abreast of these changes. There is an entirely new chapter on the antibiotics, and the chapter on poliomyelitis has been rewritten. Throughout the text numerous changes were noted, emphasizing treatment in particular. The revision still retains its readability and compactness, and will undoubtedly continue to hold its place as one of the best practical discussions of the common contagious diseases.

The Surgery of Childhood for Nurses. Raymond Farrow, B.Ch.(Oxon.), F.R.C.S. (Eng.), Baltimore, 1956, Williams & Wilkins Co., 314 pages. Price $6.00.

In this text for nurses in charge of the surgical patients in a children's hospital, the author has stressed the fundamental features of the surgical conditions commonly encountered. It is an English text, and some of the drugs used are unknown to American physicians under the trade name used. Otherwise it is a practical, well-written text, and a useful book for the nurses' library and the surgical ward. Many surgeons will have their own nursing techniques for particular conditions, but, in general, the discussion is sound.

Epileptic Seizures. Edited by John R. Green, M.D., and Harry F. Steelman, M.D., Baltimore, 1956, Williams & Wilkins Co., 165 pages. Price $5.00.

The proceedings of a meeting of the Western Institute on Epilepsy held in Phoenix, Arizona, November, 1955. The papers and discussions cover many of the phases and problems of the disease: diagnosis, medical and surgical treatment, educational problems of the epileptic, and employment and rehabilitation aspects.

Year Book of Pediatrics, 1956-1957 Series. Edited by Sydney S. Gellis, Chicago, 1956, The Year Book Publishers, Inc., 480 pages. Price $6.75.

This year's volume follows the form of the previous annual editions. Abstracts are from articles appearing in June, 1955, through May, 1956. There is apparently an increase in the number of articles abstracted from the foreign literature. Many of the papers abstracted have been referred for comment to physicians with a particular knowledge and interest in the topic.

Educating Spastic Children. F. Eleanor Schonell, M.A., Ph.D., New York, 1956, Philosophical Library, 242 pages. Price $6.00.

This is an interesting discussion of the many problems involved in the education of the spastic child. The author has a broad background as she was a research fellow at the spastic center of the Birmingham, England, pediatric group, and subsequently spent time in the spastic centers in Canada, the United States, and New Zealand. In recent years she has been associated with the spastic centers and work in Australia. It combines scientific research with the practical problem of the spastic child. After chapters defining the problem and the result of survey studies, the author takes up the educational and scholastic problems, and finally the psychologic and social aspects.

Clinical Pathology, ed. 2. Benjamin B. Wells, M.D., Philadelphia, 1956, W. B. Saunders Co., 488 pages. Price $8.50.

A second revised edition of the text first published in 1950. It is a text for students and physicians, with the purpose of acting as a guide in the application and interpretation of clinical laboratory studies. The new edition contains many rearrangements of the material as well as new material.

The Yearbook of Modern Nursing. Edited by M. Cordelia Cowan, New York, 1956, G. P. Putnam's Sons, 446 pages.

A "yearbook" along the lines of similar annual volumes in the field of social work. It brings together the developments and trends in many phases of nursing activity during the previous year. Some 150 nurses and educators have contributed to the volume.

Diseases of the Heart, ed. 2. Charles K. Friedberg, M.D., Philadelphia, 1956, W. B. Saunders Co., 1,161 pages. Price $18.00.

The first edition published in 1949 has been extensively revised and rewritten to keep pace with the rapid advances in this field. Special emphasis has been placed on the pathologic physiology of cardiac disorders and the newer methods for measuring circulation.

The Merck Manual, ed. 9. Rahway, N. J., 1956, Merck & Co., Inc., 1,870 pages. Price $6.75.

The manual is similar to previous editions. It has been extensively revised to include the new methods of use in diagnosis, and particularly the numerous new advances in the fields of antibiotics, steroid therapy, and the tranquilizing drugs. A number of special features have been introduced.

Dictionary of Poisons. Ibert and Eleanor Mellan, New York, 1956, Philosophical Library, 150 pages. Price $4.75.

This is a handbook on poisons for the family library rather than for physicians. The material is arranged alphabetically by the various poisons, giving the immediate treatment. The specific discussion of nearly every poison ends with the phrase, "Call a Physician!" A useful, sound, and unusual addition to the many volumes designed for the home medical library.

Editor's Column

THE TRADE-NAME-FOR-A-DRUG DILEMMA

WITH the tremendous output of new drugs by the pharmaceutical companies in recent years, the use of a copyrighted trade name to designate each specific drug has created a somewhat burdensome problem for the practitioner. A few years ago a colleague was asked his reasons for retiring from an active practice. He replied he could not remember the names of all these new drugs and many were so alike that he was certain before long he would make a mistake and perhaps kill a child. While we are certain that there were other reasons, his unusual reply emphasized a matter that is bothering the practitioner.

There are several reasons for the use of trade names. Prominent is the commercial value, as a well-established trade name can bring considerable monetary return to the owner. "Aspirin" as a trade name for acetylsalicylic acid was a profitable possession of one company for many years, and became a household word through advertising. During these years acetylsalicylic acid tablets could be bought at the drugstore at a much lower price than aspirin, and were manufactured by a number of chemical companies. When the copyright on the term "aspirin" expired, the manufacturing and distributing companies immediately began to call acetylsalicylic acid, aspirin. Recently the Monsanto Chemical Company, which manufactures chemicals but does not distribute them, held a scientific symposium on the pharmacology and use of the salicylates, in commemoration "of the production during the month of November (1956) of the company's 100 millionth pound of aspirin." The commercial value of a well-established trade name is too well known to require further discussion.

Another reason for trade names for drugs is that it relieves the physician of trying to remember the long technical chemical names for the many new and important products that have been introduced in recent years. We imagine that if benzalkonium chloride had to be remembered and spelled each time a prescription was written, most inflamed eyes would be irrigated with a boric acid solution.

Trade names were not a problem to the physician twenty to thirty years ago, but in recent years their number has multiplied like bacteria in a culture medium and no longer have much meaning. In fact, the drug companies have great difficulty in selecting catchy, easily memorizable names for many of their products. One company has even turned to one of the modern "electronic brain" machines for help in this respect. Prefixes, roots, suffixes, along with other data, are fed into the machine, the button pushed, and out pours a large number

of names from which a selection can be made. Many copyrighted trade names are so alike that it is almost impossible for the busy practitioner to remember which is which. A few examples of this alikeness are Desitin, Desenex; Elkaserp, Elkosin; Butazolidin, Butasal sodium; Diaperine, Diamox; Bonadoxin, Bonamine; Vioform, Viofort; Compazine, Compocillin. This is what was referred to by our retired colleague.

This is another aspect to the trade-name confusion which is of particular interest to the Editor. It is a long-established rule that when a trade name is used in a medical journal advertisement, the technical or scientific name of the drug must also appear. This rule had its origin many years ago before the era of synthetic chemical drugs and when trade names were used for products containing such relatively simple ingredients as acetylsalicylic acid, iron, and the like. The rule was sound and made sense, as otherwise the physician would be prescribing a "proprietary" preparation when he prescribed by a trade name. We have been wondering more and more as we look over current advertising copy about two aspects.

Do the chemical names of the modern drugs (which the advertising copy writers for some reason or other often put in such small type that a magnifying glass is almost required to read it) really mean anything to the average practicing physician, or has he simply been impressed by a plausible detail man that A's preparation of X is the best antihistamine, or B's preparation of Y is the best anticonvulsive, etc.? Most practitioners with whom the question has been discussed frankly admit that the chemical name has little meaning for them as regards the pharmacology of the drug.

A second somewhat related question is whether or not the physician, when he prescribes by a trade name, knows the drug by its chemical or technical name, and whether he automatically associates the two. To satisfy our curiosity on this point, a list of twelve drugs by chemical names was drawn up from advertisements appearing in the November issues of the JOURNAL, *Pediatrics*, and the *J. A. M. A.*, and sent to a number of pediatricians in various parts of the country, asking them to write down *offhand* the trade names of the drugs. To make it easier one product included in the list had three trade names used by different firms for the same drug, and another was distributed and advertised by two firms under different trade names. The replies disclosed that only an average of 31 per cent of the trade names were known (3.7). The highest score was 8 (66.6 per cent) and the lowest, 1 (8.4 per cent). However, 2 of the 12 were known by over 90 per cent, and 2 others by over 75 per cent. Of the remaining 8 on the list, the recognition fell to 11 per cent. Thus only one-third of the technical chemical names were fairly well associated with the trade names, while two-thirds were apparently quite unknown.*

There is no particular moral attached to all of this. It simply points out that with the tremendous and constantly increasing number of new drugs developed in recent years, a

*The questionnaire which the Editor imposed on some forty of his friends brought forth many comments. In order that the reader may try out his own knowledge if he so desires, the list appears on page 82 of the advertising section. No prizes are offered.

problem has been created for the practitioner by the highly competitive pharmaceutical companies seeking to establish new drugs by trade names.

We do not believe that trade names should be abolished, nor that the pharmaceutical research which leads to new drugs, and in turn to new trade names, be lessened. Further we believe the scientific names should appear in medical journal advertisements along with the trade names, despite the fact that seemingly they mean little to the physician. However, a perplexing situation exists involving the exploitation of drugs by trade names. Perhaps someone wiser than the Editor can suggest a way out.

THE PHYSICIAN AND THE MENTALLY RETARDED CHILD

IN RECENT years there has been an increasing interest in the mentally retarded child. Many of our children's hospitals have developed special clinics for the study of the retarded child as a part of their educational and community responsibilities.

The problem, while not new, is a large one, but there is no accurate information as to its magnitude. Estimates vary from 2 to 4 per cent of the population—3 to 6 million individuals. Fortunately there is agreement that approximately 75 per cent of the mentally retarded belong to the "mild group," who, with proper care, can make a fairly satisfactory adjustment to community life, while only 5 per cent belong to the severely retarded group and are unteachable.

There is general agreement further that the physician occupies a potentially strategic position in the field, as it is the physician to whom the parents first turn for diagnosis and help. His attitude and advice at this time play a most important, often determining, part in the future of the particular child, as they influence the early reactions of the parents to the problem that must be faced. He is in a position where he can be of great help or do great harm. It is not an easy task that faces him in the specific case. Just how should these particular parents be told; how much can be definitely stated as to the child's future; should home or institutional care be suggested; should his attitude in the particular case be one of bluntly stating the facts or temporizing? These are some of the problems he cannot avoid. He is faced with a far more important medical or health problem than when the patient presents a strictly medical condition such as a pneumonia.

We are happy to be able to present in this issue three papers and a panel discussion presented at a symposium held at the Children's Hospital in Los Angeles, April 9, 1956, aided by a grant from the California State Department of Health, on the theme of the role of the physician in the problems associated with mentally retarded children. A fourth paper presented by Bakwin, "Informing the Parents of the Mentally Retarded Child" appeared in the October, 1956, issue of the JOURNAL (page 486).

They contain excellent advice based on the experience of medical leaders in this field.

Quite by chance, as Profiles are published in the order received, in this same issue appears a Profile of John Thomson of Edinburgh. Dr. McNeil tells of Thomson's great interest in and work for the mentally retarded child. From 1904 until his death in 1926 he carried on singlehanded what came to be known in Edinburgh as the "Mental Clinic." The interesting description of the clinic of this pioneer worker in the field is in vivid contrast to the clinics being established today, with a staff of psychiatrists, clinical psychologists, and social workers. It is as fine an example as we have run across of what a man who is both physician and humanist can accomplish by individual effort. Could it be that our generation is overemphasizing the importance of group efforts over the work of the individual?